Stroke-Induced Sudden-Autonomic Death
Areas of Fatality Beyond the Insula

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See related article, pages 2425–2431.

Stroke is the third leading cause of death. Fatal outcome has been primarily related to acute or chronic complications of stroke-induced executive deficits, such as muscle weakness, swallowing disorders, respiratory dysfunction with pneumonia, or cardiac complications.

Only during the last 10 or 15 years has there been an increasing interest in and knowledge of associations between cerebral lesions and altered influences of the central autonomic nervous system on cardiovascular and respiratory function. Oppenheimer et al. suggested a role of the insular cortex in the pathophysiology of sudden death. The group extensively assessed topographically distinct interactions of the left and the right insular cortex with heart rate and blood pressure control. There was agreement that insular cortex lesions essentially contribute to clinically relevant alterations of cardiovascular control.

In this issue of Stroke, Rincon and coworkers present an analysis of associations between ischemic stroke location and fatal cardiac outcome, based on the epidemiological data of the Northern Manhattan Stroke study (NOMAS). Considering neurological syndromes and neuroimaging findings, the authors analyzed outcome during a 5-year follow-up period. Mortality rates or nonfatal myocardial infarctions, and particularly sudden unexpected or unwitnessed death, were associated with the location of brain infarctions. Apart from age, male gender, the National Institutes of Health Stroke Scale (NIHSS), and a history of coronary artery disease, the authors identified infarct locations in the frontal, parietal, temporal lobe, and the insula as predictors of cardiac death as well as composite outcome of cardiac death or myocardial infarction.

The frontal lobe, especially the ventromedial prefrontal cortex (VMPFC), has significant modulating effects on cardiovascular responses to emotional stimuli. Unilateral VMPFC lesions compromise responses to even mild emotional stimuli. Left VMPFC lesions result in dampened heart rate or blood pressure adjustment to visual emotional stimuli, whereas right-sided VMPFC lesions bear a risk of exaggerated cardiovascular responses with paradoxical heart rate and blood pressure increase. Similarly, lateralized effects on resting cardiovascular modulation have been observed after insular stroke.

Zamrini et al. and Hilz et al. observed a hemispheric dominance of sympathetic or parasympathetic activity in temporal lobe epilepsy patients who underwent hemispheric inactivation during the so-called WADA testing procedure before epilepsy surgery. In these patients, left-hemispheric inactivation increased sympathetic cardiovascular modulation whereas right-hemispheric inactivity furthered parasympathetic activity. After left- or right-hemispheric ischemic stroke, Klingelhofer and Sander observed autonomic changes that were opposite to those in temporal lobe epilepsy patients with hemispheric inactivation but suggested right-sided dominance for sympathetic effects after hemispheric stroke. This discrepancy might be explained by a functional hypoactivity of lesioned autonomic centers after stroke while the same centers may be upregulated in temporal lobe epilepsy patients because of spreading discharges from epileptogenic foci. The net results would be diametrical changes in cardio-vagal balance of heart rate of blood pressure.

Tailored resection of anterior temporal lobe areas lowers sympathetic cardiovascular activation, which may be beneficial in seizure patients with presurgically increased risk of tachyarrhythmias but might also explain a role of the temporal lobe in unexpected death after stroke. An ischemia-induced decrease in sympathetic temporal lobe contribution to autonomic balance is likely to result in a shift toward cardio-vagal predominance which then facilitates bradycardia or even asystole.

Surprisingly, Rincon and coworkers could not confirm a dominant association of the insular cortex with increased mortality. Some of the discrepancy to findings by Oppenheimer and coworkers might be due to the fact that Oppenheimer deduced their conclusions from insular cortex stimulations in rodents, ie, from activation of brain areas that may be silent or dysfunctional after stroke. Thus, the hemispheric autonomic lateralization seen with stimulation might be reduced or inverted in stroke patients because of a predominance of autonomic activity from the nonischemic hemisphere. Of course, these considerations of autonomic balance are a rather mechanistic approach that cannot reflect the complex interactions of autonomic feed-forward and feedback loops, still poorly understood circuitries and multiple influences from external, endocrine, neuronal, and peripheral input channels.

According to Rincon et al, infarctions involving the left parietal lobe seem to be associated with a particularly increased risk of cardiac events and a 4.45 hazard ratio of

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cardiac death. The authors found similarly high risk of death after right parietal lobe infarctions when infarct size was taken into account. Probably, the parietal lobe has buffering effects on the insular region which are disinhibited after loss of parietal activity. During acute stroke, discharges from the penumbra and deficient activity from ischemic neurons may add to an autonomic imbalance, whereas chronic stages are more likely dominated by deficient neuronal activity. Only invasive electroencephalographic recordings might reveal whether cardiovascular events such as myocardial infarction or death are related to paroxysmal cerebral hyperactivity or result from centrally mediated bradyarrhythmia.19,20 In pentylenetetrazol treated epileptic cats, Lathers et al demonstrated a “one-to-one” transmission of cerebral epileptogenic discharges onto the heart.23 Such bursts of activity might account for myocardial infarctions as observed in the NOMAS study and described in many previous publications.24 Sympathetic overstimulation of the heart may cause increases in troponin I, diffuse myofibrillar necrosis, perivascular and interstitial fibrosis as well as myocyte vacuolization in the absence of ischemic heart disease.24–26 However, it so far remains to be speculated whether lack of outflow toward centers of cardiovascular modulation or excessive activation of master controllers of cardiovascular modulation, such as the hypothalamus or amygdala, accounts for the high rate of fatalities in NOMAS after 4 years.

Rincon et al made a remarkable observation that the “lethal” contribution of the parietal lobe is not apparent during the first 30 days after stroke, but only with long-term follow-up examination. Recently, the group of Teasdale and coworkers reported an excessively high rate of sudden death in patients who had experienced mild traumatic brain injury years ago.27 The authors report an up to 7-fold increased risk of death in patients who had experienced a mild traumatic brain injury for up to 7 years.27 Evidently, the autonomic control areas assuring cardiovascular stability and survival comprise a fragile system of cerebral regions with so far poorly understood physiology. The NOMAS study does not explain why the parietal lobe lesions are so critically involved in death. However, the study challenges stroke researchers to address not only the urgency of instantaneous stroke treatment but also to further explore the “heart-brain” or “brain-heart” interaction. The NOMAS data demonstrate that time is not only brain but also heart. Oppenheimer and coworkers described the insular cortex as an area associated with increased risk of sudden death.9 Perhaps, the parietal lobe contains areas that are essential for survival. Although acute rescue and recovery dominate the emergency treatment of stroke patients, the need for long-term cardiovascular restabilization and protection against sudden death has, so far, not been adequately recognized. Rincon et al are to be commended for their analysis because it underlines the urgency to identify stroke patients at risk of a “broken heart” during early stages of disease in order to identify pathophysiologic patterns and institute long-term protective treatment.

Disclosures

None.

References

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