Stroke is among the leading causes of mortality [1, 2]. In previous years, causes of mortality were thought to be related to the acute or chronic deficits resulting from the stroke induced motor, sensory, executive dysfunction, such as swallowing disorders, respiratory dysfunction or cardiac complications [3, 4].

The recent, striving development in autonomic research, however, has shown that dysfunction of areas contributing to the central regulation of the autonomic nervous system may account for secondary complications in stroke patients, not only during the acute but also during the chronic phase of disease [5–7].

Vladimir Hachinski and his group, particulary S.M. Oppenheimer, D.F. Cechetto and Hachinski himself had investigated the possible role of the insula in increased risk of cardiovascular complications and mortality rates after stroke (8–10). The group studied the topographic correlations between specific lesions or stimulations of the left and right insula and cardiovascular control [11]. Today, there is no doubt, that hypoactivity or hyperactivity of insular regions has effects on cardiovascular control [8].

In a follow-up analysis of the Northern Manhattan Stroke Study (NOMAS) [12, 13, 14], Rincon et al. studied the risk of cardiac death during five years after acute stroke in relation to the acute stroke location [12, 13, 14]. The authors found that the location of the stroke may be a predictor of post-stroke mortality rate, of sudden unexpected death and of non-fatal myocardial infarctions [14]. In addition to age, male gender, the severity of clinical deficits assessed by means of the National Institutes of Health Stroke Scale (NIHSS), and a history of coronary artery disease, further predictors of post-stroke mortality, sudden death or non-fatal myocardial infarctions were stroke lesions in the frontal, parietal, temporal lobe, and insular cortex [14]. The five year follow-up of the NOMAS patient population, Rincon et al. particulary emphasised the high increase of the hazard ratio for cardiac death in patients who had an infarction within the left parietal lobe [14].

Our own research showed relevance of an adequate balance between the left and right hemisphere and integrity of various brain regions. The ventromedial prefrontal cortex (VMPFC) is essential for the adequate modulation of heart rate and blood pressure responses to emotional activation [15]. Even mild emotional stimuli such as the presentation of slightly positive or happy images or slightly negative or unhappy images result in compromised cardiovascular responses if the patient had a unilateral lesion of the VMPFC [15]. We showed that a lesion in the left VMPFC results in heart rate and blood pressure changes upon emotional stimulation that are similar to the responses in healthy persons but significantly dampened [15]. In contrast, lesions within the right-sided VMPFC are associated with paradoxical and exaggerated heart rate and blood pressure responses to visual emotional stimulation [15]. The effects of a lesion that is restricted to only one hemisphere has also been shown after insular stroke [11, 16–18]. Differences between hemispheric effects on autonomic cardiovascular modulation have been shown by Zamrini et al. [19] and Hilz et al. [20] in patients with drug-refractory temporal lobe epilepsy who needed neuropsychological assessment of the hemispheric speech- and memory-dominance before epilepsy surgery, and, therefore, underwent a so-called Wada test. This is a unilateral inactivation of one hemisphere and then the other hemisphere [20]. The amobarbital inactivation of the left and then the right hemisphere showed that left-hemispheric inactivation augments the sympathetic outflow to the heart and vasculature, while inactivation of the right hemisphere enhances parasympathetic outflow...
Klingelhöfer and Sander showed significant autonomic changes after hemispheric stroke [16] and demonstrated effects that seemed to be opposite to those seen in our temporal lobe epilepsy patients after hemispheric inactivation. From their work, Klingelhöfer and Sander [16] concluded that the sympathetic activity dominates after a right-hemispheric stroke. We can only speculate that this discrepancy between findings in epilepsy and post-stroke patients is related to a functional decrease in neuronal activity in autonomic areas involved in the stroke territory, while there may be a functional hyperactivity of central autonomic areas in temporal lobe epilepsy due to the spreading of epileptogenic discharges even during interictal periods [20]. At any rate, there is a difference between sympathetic and parasympathetic modulation in the left and right hemisphere and this difference results in a significant imbalance of the sympathetic and parasympathetic nervous system and its effects on heart and blood pressure if there is a hemispheric lesion, focus or hyperactivity.

We also showed that removal of the anterior temporal lobe in patients who need epilepsy surgery due to medication-resistant seizures results in a reduction of sympathetic outflow to the heart and to resistance vessels that control blood pressure [21]. While the reduction in sympathetic activity may be quite beneficial in epilepsy patients who frequently have paroxysms of tachycardia or tachyarrhythmias [21], decrease in sympathetic outflow due to stroke-induced tissue loss might result in more parasympathetic activity and consequently promote slowing of heart rate or possibly even asystole [15, 20, 21]. In their five year follow-up study, Rincon et al. did not find a dominant role of the insula itself regarding increased mortality rates in the NOMAS population [14]. Perhaps the difference is again due to the fact that Oppenheimer and colleagues [22] made their observations from insular stimulations in animals while the conclusions drawn by Rincon et al. from the NOMAS data are based on stroke-induced neuronal loss but not on the activation of neuronal tissue [14]. The NOMAS data suggest a particularly high risk of cardiac events with a hazard ratio of cardiac death as high as 4.45 if the left parietal lobe is involved in the stroke [14]. In an editorial comment to the Rincon study, we concluded that the parietal lobe might have buffering effects on the insula and that such effects may be disinhibited after stroke-induced loss of parietal discharges [23]. We assume that there is also a significant difference between the chronic stage after stroke and the acute stroke stage with penumbra tissue adding to the deficiency from ischemic neurons [23, 24].

So far, the pathomechanisms leading to myocardial infarction and death after stroke still need to be clarified. However, the effects of the brain on the heart have been demonstrated in an animal study by Lathers and co-workers [25]. The group saw a “one-to-one” transmission of epileptic brain discharges onto the heart in epileptic cats [25]. Such activity may cause myocardial damage and infarction that have been described in previous publications [26]. Overactivity of the sympathetic system results in increased troponin I levels, diffuse myofibrillary necrosis, perivascular as well as interstitial fibrosis and vacuolization of myocytes [26-28].

We assume that a disturbance of the complex and widespread central autonomic nervous system - that comprises basically all brain regions [24] – facilitates a development of cardiac irregularities, rhythm abnormalities, inadequate swings in blood pressure and impairment of baroreflex sensitivity.

In patients who had suffered a mild traumatic brain injury, without macroscopic or histologic brain lesions, Teasdale and co-workers found a long-term increase in the risk of sudden unexplained death [29]. During this seven year follow-up study, even patients who only had a history of mild brain injury had a seven times higher risk of death than in the average population [29]. We speculate that this increase in risk after brain injury, be it due to trauma or stroke, is related to a compromised interaction of the many centers within the central nervous system that assure fine-tuning of cardiovascular function [24]. While Oppenheimer and colleagues identified the role of the insula in cases of increased cardiovascular risk [9], other studies demonstrate that many brain areas contribute to a balanced interaction between the heart and the brain.

Modern neurology improves the survival rate and the quality of life of acute stroke patients. However, the significantly increased and prevailing risk of cardiovascular complications and even death [1–4, 14] has not yet been addressed to the extend it deserves. Long-term survival of stroke patients will improve when we have gained a better understanding of the interaction between autonomic centers within the central nervous system and the cardiovascular system itself [7, 24].

Therefore, detailed studies assessing the sympathetic-parasympathetic balance, over- or under-activity of autonomic function and identifying brain regions of particular autonomic risk are of utmost importance and deserve intensified support. Very likely, such research will not only result in a better understanding of central autonomic cardiovascular control but will also improve survival and recovery of stroke patients in general.
REFERENCES