

## Disorders of the Autonomic Nervous System after Hemispheric Cerebrovascular Disorders: an Update

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### Abstract

Autonomic and cardiac dysfunction may occur after vascular brain injury without any evidence of primary heart disease. During acute stroke, autonomic dysfunction, for example, elevated arterial blood pressure, arrhythmia, and ischemic cardiac damage, has been reported, which may hinder the prognosis. Autonomic dysfunction after a stroke may involve the cardiovascular, respiratory, sudomotor, and sexual systems, but the exact mechanism is not fully understood. In this review paper, we will discuss the anatomy and physiology of the autonomic nervous system and discuss the mechanism(s) suggested to cause autonomic dysfunction after stroke. We will further elaborate on the different cerebral regions involved in autonomic dysfunction complications of stroke. Autonomic nervous system modulation is emerging as a new therapeutic target for stroke management. Understanding the pathogenesis and molecular mechanism(s) of parasympathetic and sympathetic dysfunction after stroke will facilitate the implementation of preventive and therapeutic strategies to antagonize the clinical manifestation of autonomic dysfunction and improve the outcome of stroke.

### Keywords

Autonomic dysfunction; heart rate variability; insula; stroke

### Introduction

Cerebrovascular disorders are a major cause of morbidity and death in the United States and Europe [1–10]. Sudden death following acute stroke has been reported, but is beyond what is expected from a concomitant coexisting coronary artery disease [11]. Several studies have demonstrated that cardiac dysfunction may occur after vascular brain injury without any evidence of primary heart disease [12–16]. Furthermore, during acute stroke, autonomic dysfunction, for example, elevated arterial blood pressure, arrhythmia, and ischemic cardiac damage, has been reported, which may hinder the prognosis [17–23]. Autonomic dysfunction after a stroke involves the cardiovascular, respiratory, sudomotor, and sexual systems. Although the exact mechanism is not fully understood, several studies suggest an anatomical asymmetry between the right and left cerebral hemispheres in the modulation of autonomic nervous system activity of the central nervous system (CNS). It is well known that cerebrovascular diseases, particularly ischemic stroke, can alter the function of the autonomic sys-

tem both acutely and chronically [24–26]. These autonomic changes can be cardiac, respiratory, sudomotor, or sexual in nature [27] and can be detected clinically and electrophysiologically [14]. Some of these changes have an impact on the morbidity and mortality in patients suffering a stroke [3,26]. Multiple and different anatomical regions of the brain have been suggested to be involved, but the exact pathogenesis and mechanism(s) leading to these changes is not fully understood [24,28]. In this review paper, we will discuss the anatomy and physiology of the autonomic nervous system and the mechanism(s) suggested to cause autonomic dysfunction after stroke. We will also review the spectrum of autonomic dysfunction associated with stroke and the influence of hemispheric damage location on the occurrence of autonomic dysregulation.

## Central regulation of the autonomic nervous system

Central nervous system control of the autonomic nervous system involves several interconnected structures distributed throughout the neuraxis [29]. The central autonomic network is organized into closely interconnected spinal, bulbopontine, pontomesencephalic, and forebrain levels. The spinal level mediates segmental sympathetic or sacral parasympathetic reflexes. The bulbopontine level is involved in the reflex control of respiration and circulation. The pontomesencephalic level controls pain modulation and integration of behavioral responses to stress. The forebrain level includes the hypothalamus and the anterior limbic circuit, which includes the insula. The forebrain is involved in goal-related autonomic and endocrine responses for homeostasis and adaptation [29].

The insular cortex integrates visceral, pain, and temperature sensation [29–31]. It is divided into an anterior and a smaller posterior part. The posterior part of the insula has a viscerotropic organization [32] and receives input from the gustatory, visceral, muscle and skin receptors via the thalamus and projects to the right anterior insula, which integrates this input with emotional and cognitive processing to convey the conscious experience of bodily sensation [29,30]. The insula carries a visceromotor function controlling sympathetic and parasympathetic outputs via a relay in the lateral hypothalamus.

The anterior cingulate cortex has extensive connections with the insula, prefrontal cortex, hypothalamus, amygdala, and brain stem and controls sympathetic and parasympathetic function [29,33]. The hypothalamus is involved in homeostasis and adaptation by integrating autonomic and endocrine responses [29]. Several brain stem areas are involved in autonomic nervous system control, including the periaqueductal gray matter of the midbrain, the parabrachial nucleus, and several parts of the medulla [29]. The autonomic output of the CNS is divided into sympathetic and parasympathetic. In addition to thermoregulation, the sympathetic output is crucial for the maintenance of arterial pressure and regional blood flow.

The sympathetic output originates from the preganglionic neurons located in the thoracolumbar spinal cord at the T1-L2 levels. These neurons are controlled by premotor neurons in the brain stem and hypothalamus to initiate appropriate responses to internal and external stressors such as exercise and dehydration [29]. The rostral ventrolateral medulla and lateral hypothalamic area,

as well as other brain stem regions, host the main source of premotor sympathetic innervation [29].

The parasympathetic system output is formed by the vagal and sacral outputs and is responsible for mediating reflexes activated in an organ-specific fashion. The vagus nerve is the main parasympathetic innervation of the thoracic and abdominopelvic viscera. Eighty percent of vagal fibers are afferents with cell bodies originating from the superior and inferior vagal ganglion [34]. The efferent fibers of the vagus nerve, preganglionic visceromotor fibers, originate from the dorsal motor nucleus of the vagus (DMV) and the nucleus ambiguus in the medulla oblongata [34]. The nucleus of the tractus solitarius (NTS), the nucleus of the spinal tract of the trigeminal nerve, medial reticular formation of the medulla, area postrema, DMV, and the nucleus ambiguus host vagus nerve afferent projections [34]. The vagal parasympathetic output to the heart originates primarily from the ventrolateral portion of the nucleus ambiguus via the cardiac ganglia [29]. Output of the nucleus ambiguus is activated by the NTS during the baroreflex and inhibited during inspiration. The nucleus ambiguus output inhibits sinoatrial node automatism [29]. The sacral parasympathetic output originates from neurons located at the S2–S4 segments of the sacral spinal cord and plays a critical role in the control of micturition, defecation, and sexual function [29,35].

The baroreflex and baroreceptors, located in the carotid sinus, aortic arch, and right atrium, are involved in blood pressure control and are activated by beat-to-beat fluctuation of systemic blood pressure [36]. Receptors located in the carotid sinus and aortic arch are sensitive to reduction in pulse pressure, whereas receptors of the right atrium are more sensitive to alteration in blood volume [37]. The NTS and the ventrolateral medulla receive afferents from the baroreceptors and send efferents to the insula and other autonomic centers for further processing. Brain stem and hemispheric cerebrovascular damage may affect the baroreflex causing blood pressure instability [36].

## The spectrum of autonomic dysfunction secondary to stroke

Autonomic dysfunction is a common complication of cerebrovascular disorders but is not limited to cardiovascular manifestations. Autonomic dysfunction secondary to stroke extends to sudomotor, vasomotor, impotence, and urinary dysfunction [26].

## Heart rate variability

Heart rate variability (HRV) has been used extensively to assess autonomic dysfunction following ischemic stroke [38–45]. HRV is defined by the variation in heart beat intervals or correspondingly in the instantaneous heart rate, which is due to an autonomic neural regulation of the cardiocirculatory system [46]. It is a reflection of the amount of heart rate fluctuation around the mean heart rate and reflects the balance between the sympathetic and parasympathetic nervous systems. Several methods used to analyze HRV are based on time domain analysis, frequency domain analysis, and nonlinear methods of analysis [46].

In time domain analysis, the following indices are used: mean heart rate, standard deviation of normal-to-normal interbeat intervals (SDNN), and root mean square of square sum of adjacent normal-to-normal interval difference (rMSSD). SDNN reflects overall heart rate variability, whereas rMSSD correlates with vagal-mediated control [38].

Frequency domain analysis is based on spectral analysis of fluctuation of autonomic tone. Spectral analysis splits a signal into its underlying frequencies. Parasympathetic modulation of heart rate is more pronounced at a frequency range of 0.15–0.5 Hz, the high-frequency range (HF). At a frequency ranging from 0.04 to 0.15 Hz, the so-called low-frequency range (LF), HRV is controlled by a dual contribution of sympathetic and parasympathetic nervous systems. The very low-frequency range (VLF) corresponds to frequencies less than 0.04 Hz and reflects the integrative effect of various controllers such as vagal to humoral effects [38,47].

In a prospective study, Korpelainen *et al* analyzed the HRV of 31 consecutive patients with hemispheric brain infarction in the middle cerebral artery territory, during the acute phase and again at 1 and 6 months after the initial event [48]. All studied patients had no manifestations of primary cardiovascular disease and were not on any medications that may interfere with autonomic function. In the acute phase after infarction, all the time domain and frequency domain markers of HRV in stroke patients were significantly lower than those of control subjects. It was noted that the severity and size of the infarct, but not the location, were associated with lower HRV. This difference was maintained 1 and 6 months after the onset of acute stroke. The side of cerebral hemisphere involved did not alter HRV. The authors concluded that hemispheric brain infarction seems to cause a significant long-lasting dysfunction of the autonomic cardioregulatory system. This dysfunction

reflects both sympathetic and parasympathetic autonomic failure and may be associated with damage to the insular cortex and its neural connections involved in cardiovascular regulation [48].

In another prospective study, 103 patients with a first ischemic stroke were evaluated for HRV. The infarct was on the right side in 49 patients (47.5%) and on the left in 54 patients (52.5%). The insula was involved in 33 patients with right-sided stroke (67.3%) and in 36 patients with left-sided stroke (66.6%). Analysis of patients with ischemic stroke revealed a significant decrease of all HRV components and higher LF/HF ratio values when compared with controls. Patients with right-sided infarcts involving the insula showed significantly lower SDNN and rMSSD RR interval values and higher LF/HF ratio values than all other stroke patients. The study also demonstrated that both ventricular and supraventricular arrhythmias were found to be more frequent and complex in all subgroups of stroke patients than in controls. Patients with right-sided insular ischemia had a higher prevalence of arrhythmia than those with left-sided hemispheric stroke [14].

HRV was used by Chien-Fu Chen *et al* to study the relationship between stroke location and cardiac autonomic dysfunction [49]. In this prospective study, 75 consecutive stroke patients and 81 matched controls were evaluated. The stroke group was divided into three subgroups: 28 had right-hemispheric infarctions (RH), 29 had left-hemispheric infarctions (LH), and 18 had brainstem infarctions. Frequency domains of LF, HF, and HF% in stroke patients were significantly lower than those in controls, while values of LF% and LF/HF were significantly higher. Further analysis demonstrated significant differences between patients with brain stem infarctions and controls in LF, HF, HF%, and LF/HF, and between patients with LH and controls in LF%, HF%, and LF/HF. These findings pointed to an imbalance between the sympathetic and parasympathetic activity during the acute phase of ischemic stroke [49], supporting the previous findings of sympathetic hyperfunction unbalanced by parasympathetic failure following a stroke [50].

Autonomic dysfunction has been associated with unfavorable cardiac complications during the acute phase of stroke [51–54]. Based on the reduction of HRV during ischemic stroke and its value as a prognostic factor during myocardial infarction and heart failure, Mäkikallio *et al* evaluated the prognostic significance of HRV during acute ischemic stroke [55]. A series of 84 patients with an acute first-ever ischemic stroke were enrolled in the study and were followed for 7 years. During the follow-up period, 39% of the patients died. Among all the

variables analyzed, abnormal long-term HRV measure power-law slope  $\beta$ , an exponent that reflects an altered distribution of spectral characteristics over ultra and very low-frequency bands, was the best univariate predictor of death [55]. Power spectral analysis of HRV was used to test whether patients with large atherosclerotic infarctions have different autonomic dysfunction properties than patients with lacunar infarcts. The group with large atherosclerotic infarction had lower HF power, lower normalized HF, higher normalized LF power, and higher ratio of LF to HF than both the lacunar stroke and control groups. These findings demonstrate that the large atherosclerotic stroke group had lower parasympathetic activity and higher sympathetic activity than the lacunar stroke group, and that depressed parasympathetic activity was associated with an increased risk of worse early outcome, as was confirmed in a recent study [56].

HRV indices were used to evaluate the interaction among the CNS, the regulation of the immune response, and cardiac autonomic control after ischemic stroke. Subacute infection could be predicted in patients without clinical or paraclinical signs of infection in the acute period using different HRV indices [38]. HRV suppression was used to document the imbalance between the adrenergic and cholinergic systems with prevalent sympathetic activity during the first 24 h of an acute stroke. Increased incidence of arrhythmia and elevated blood pressure paralleled HRV suppression during the same time period [17].

During a period of 18 to 43 months after a lacunar stroke, Dutsch *et al* used HRV indices to evaluate cardiovascular autonomic function and demonstrated an impairment of autonomic function with reduction of parasympathetic tone compared to controls [47]. Furthermore, the study reported that right-sided infarcts had a tendency toward increased sympathetic cardiac modulation. It was concluded that, irrespective of the side of the cerebral infarct, postacute stroke patients showed a parasympathetic cardiac deficit. Additionally, sympathetic modulation was increased in patients with right-sided stroke. The unopposed sympathetic stimulation may explain the increased risk of cardiac arrhythmia after a lacunar stroke [47].

### Abnormal heart rhythm and cardiac death

Hemispheric stroke has been associated with increased risk of cardiac arrhythmia [39,41,48,57–58]. The reported incidence of arrhythmias following stroke is higher in studies using 24-h Holter monitoring compared with electrocardiogram (ECG) recordings. To study the

occurrence of arrhythmia after stroke, Korpelainen *et al* enrolled 31 consecutive patients with hemispheric cerebrovascular accidents in the acute phase and at 1 and 6 months after the event, along with 31 age- and sex-matched healthy control subjects [48]. Each subject underwent 24-h ECG recordings during the acute phase and 1 and 6 months after the initial event. Despite a significant long-lasting damage to the cardiovascular autonomic regulatory system, none of the patients had serious arrhythmias during the ECG recording in the acute phase, at 1 month, or 6 months after the onset of stroke. All patients had a favorable cardiac outcome during the 6-month follow-up period. No arrhythmias, cardiac failure, or any other cardiac events were found [48].

In the Northern Manhattan Study, patients aged 40 years or older with first-time ischemic stroke were prospectively followed for the occurrence of sudden death and arrhythmia. During a median follow-up period of 4 years, 44 patients (6.7%) had fatal cardiac events. Of these, 81.8% experienced fatal myocardial infarction and sudden death [59].

On the basis of ECG recordings, Lavy *et al* reported a 52% incidence of new-onset arrhythmias following stroke in patients with no evidence of preexisting heart disease. This study also revealed that new electrocardiographical abnormalities in patients without evidence of heart disease prior to the stroke were associated with poorer prognosis [60]. Goldstein reviewed electrocardiographic records of 150 patients with acute stroke along with 150 age- and sex-matched controls and reported a significant higher number of abnormal ECGs in stroke patients compared with the controls (92% vs. 65%,  $p < 0.001$ ). The study also reported a 25% incidence of cardiac arrhythmias in acute stroke patients compared with 3% in the control group [61]. From Holter recording, Oppenheimer reported a 12% overall incidence of ventricular tachyarrhythmias after stroke compared with 3% following a transient ischemic attack. Incidences of ventricular ectopy following stroke versus transient ischemic attack were 71% and 73%, respectively; respective incidences of atrial fibrillation were 9% versus 3% [52].

### Blood pressure variability

Damage to the autonomic nervous system may occur in the acute phase of cerebrovascular diseases and affect blood pressure control. In a prospective study, the blood pressure of 44 first-ever stroke patients was recorded on admission and on days 3 and 7 afterward. In parallel, serum levels of dopamine, epinephrine, and nor-epinephrine were measured [17]. In the group of patients

with stroke and arrhythmia, systolic and diastolic blood pressure values were higher in 61.3%, 22.6%, and 16.2% on admission, 3, and 7 days after stroke onset, respectively. In the same group of patients, levels of epinephrine, nor-epinephrine, and dopamine were higher than normal on admission in 100%, 22.6%, and 71% of patients, respectively. Three days after admission, these percentages decreased to 32.3% (epinephrine) and 35.5% (dopamine), whereas there was a slight increase in nor-epinephrine level to 29%. Seven days after stroke onset, catecholamines levels returned to normal. The 24-h urinary catecholamine levels followed a similar trend. In the group of patients with stroke and no arrhythmia, systolic and diastolic blood pressure values were higher in 61.6%, 38.4%, and 23.2%, respectively on admission, 3, and 7 days after stroke onset. In the same group, changes in catecholamine levels were not observed. The study concluded that a transient alteration of the autonomic nervous system occurs during the hyperacute phase of stroke with prevalent sympathetic activity [17].

In another study, 24-h ambulatory blood pressure monitoring was performed on days 1 and 7 after hospital admission in 72 patients with acute ischemic stroke. The study demonstrated elevated blood pressure on day 1 after stroke that resolved spontaneously on day 7 [62]. Zis *et al* enrolled a consecutive series of 109 first-ever stroke patients who underwent a 24-h ambulatory blood pressure monitoring within 24 h after stroke onset [63]. The study demonstrated that the 24-h rate of systolic blood pressure variation was higher in patients with large artery atherosclerosis compared to those with lacunar or cryptogenic strokes. Furthermore, the study demonstrated that patients with a higher 24-h rate of systolic blood pressure variation were more likely to have poor outcomes at 1 year of follow-up. Moreover, each 0.1 mmHg/min increase in the 24-h rate of systolic blood pressure variation was associated with a 1.96-fold increase in the odds of a negative outcome [63]. Similarly, 24-h blood pressure ambulatory monitoring of 104 patients with acute stroke demonstrated a positive correlation between mean values of blood pressure and a poor outcome 3 months after stroke onset [64].

Alteration of blood pressure control was sustained several months after acute stroke. McLaren *et al* conducted a cross-sectional, case-control study comparing autonomic function in 76 nondemented stroke patients with 70 community-living controls aged 75 years or older. Cases were assessed, on average, 9 months following the onset of stroke. Blood pressure overshoot during valsalva maneuver was significantly lower in stroke patients ( $p < 0.027$ ). Furthermore, blood pressure

response to isometric exercise was significantly exaggerated in stroke patients ( $p < 0.007$ ) [65].

### Baroreflex sensitivity variability:

The baroreceptor reflex is the major neural mechanism for blood pressure control. Beat-to-beat variation in systemic blood pressure is the activator of baroreceptors located in the carotid arteries, cardiac chambers, and the aortic arch. Neural afferents from these baroreceptors relay information to the nucleus tractus solitarius and the ventrolateral medulla, which is further processed in the insula, medial prefrontal cortex, cingulate cortex, amygdala, hypothalamus, thalamus, and cerebellum [36]. Baroreflex sensitivity is quantified in milliseconds of RR interval duration to each mmHg of arterial blood pressure, with a normal value of approximately 15 ms/mmHg and a large interindividual difference [66]. There is an increasing evidence suggesting that baroreflex sensitivity is dysregulated during acute stroke [54,67–70]. Insular cortex damage seems to play a major role in baroreflex sensitivity during acute stroke [36,69,71]. However, controversy persists on the proposed lateralization of baroreflex control. One study demonstrated a reduction in parasympathetic and an increase in sympathetic heart rate modulation associated with right-sided acute stroke [36], whereas other studies showed that left insular lesions decrease baroreflex sensitivity significantly more than right-sided ones [72–74]. Alteration of baroreflex sensitivity has also been associated with poor stroke outcome and alteration of cerebral perfusion [36].

### Thermoregulation disorders

Several studies reported sweating dysfunction after acute hemispheric stroke [26,75–78]. In addition, several of these studies have reported hyperhidrosis on the contralateral side of stroke [76–78]. Up to 77% of patients have an asymmetric sweating pattern during the acute phase of stroke and the severity of sweating asymmetry correlates with the severity of motor deficits [26,76]. Dysregulation of the vasomotor autonomic nervous system, demonstrated by asymmetric skin temperature sensation, has also been reported after stroke [79,80]. Conflicting results of reduced and increased skin sensation in paretic limbs have been reported [81–83]. Subsequently, when more advanced technology was utilized, paretic limbs were found to be colder than the nonparetic limbs [80]. Decreased cortical and subcortical inhibitory effect on vasomotor neurons has been advanced to explain coldness of paretic limbs after stroke. This inhibition increases the vasoconstriction tone and reduces the cutaneous blood flow and skin temperature on the side opposite to the infarction [26].

### Sympathetic skin response abnormalities

Sympathetic skin response (SSR), which represents a potential generated in skin sweat glands, originates by activation of the reflex arch with different types of stimuli [84]. Zimmermann *et al* studied SSR in normal and hemiplegic limbs. Thirteen patients were enrolled and evaluated between 1 and 72 months after stroke and reported a 16% prolongation of the median SSR latency in the left compared to right hemiplegic limbs [85]. In another study, Korpelainen *et al* recorded SSR in bilateral hands in 58 patients with brain infarction along with 36 healthy control subjects. A significant decrease in latencies and amplitude of SSR in hemispheric infarction compared with the control subjects was observed [86]. A similar finding of alteration of SSR response was reported by Linden *et al*, who recorded abnormal SSR in 82.8% of patients with a cerebrovascular event [87]. The observed abnormalities of SSR after hemispheric stroke may be related to damage in the ascending and descending corticoreticular pathways or the cerebral cortex [26].

### Urogenital and gastrointestinal dysfunction

Urinary dysfunction after hemispheric stroke has been reported in several studies [88–90]. Urinary incontinence was considered a predictor of death, severe disability, and hospitalization outcome in stroke patients [90]. The prevalence of urinary symptoms 3 or 12 months following stroke was more than 80% in stroke survivors previously enrolled in the North-East Melbourne Stroke incidence study [91]. Urinary incontinence of new onset after acute stroke with impaired awareness of bladder needs was found to be a strong and independent risk factor for poor outcome 3 months after stroke. This may reflect more serious brain damage affecting sustained attention and information processing [92].

Han *et al* evaluated the urodynamic parameters in ischemic and hemorrhagic stroke patients. Ischemic stroke was associated with more detrusor overactivity and less detrusor underactivity [88]. In another study, Chou *et al* reported the urodynamic findings in 15 patients with cerebellar stroke. Detrusor overactivity occurred in 75% of patients with ischemic stroke and 28.6% of patients with hemorrhagic stroke ( $p < 0.072$ ). The study also demonstrated that voiding dysfunction in patients with cerebellar stroke is a dynamic process that changes with time [89]. Internal capsule and cortical infarcts have been more frequently associated with detrusor hyperreflexia [26].

The contribution of autonomic dysfunction has been proposed to explain the mechanism of sexual dysfunc-

tion after stroke. Decline in libido and coital frequency in men and reduction in vaginal lubrication and orgasmic ability in women are the most frequent sexual dysfunction manifestations after stroke [26]. The relationship between cerebral infarct location and subsequent occurrence of sexual dysfunction has been studied by Jung *et al*, who surveyed 109 stroke patients and 109 age-matched controls. The study reported a significant decrease in erectile function in stroke patients compared with the controls. Lesions in the right cerebellum were significantly associated with ejaculation disorders whereas left basal ganglia lesions were associated with decreased sexual desire [93].

Acute stroke is frequently associated with gastrointestinal dysfunction. Constipation was the dominant gastrointestinal symptom, reported in 25.9% of patients with acute stroke, followed by masticatory difficulty, observed in 20%. Other significant gastrointestinal manifestations included incomplete bowel evacuation, fecal incontinence, sialorrhea, and dysphagia [94]. Although the majority of these manifestations are related to immobilization and severity of stroke, impairment of autonomic innervation of the gastrointestinal tract is a potential mechanism of gastrointestinal dysfunction associated with stroke, especially in diabetic patients [26].

### The effects of cerebrovascular accidents location on autonomic dysfunction

For the past two decades, there has been an increased interest in studying the association of autonomic function alteration with hemispheric stroke locations, including the insular cortex and the frontal and parietal lobes [24,28,59,81,95–97].

#### Insular cortex

Several studies showed that the insular cortex is involved in cardiovascular and autonomic regulation [24,98–100]. Oppenheimer *et al* conducted a series of experiments in rats and were able to induce ECG changes similar to those observed after stroke [101]. Subsequently, Ay *et al* conducted a prospective study to identify regions of brain ischemia associated with myocardial infarction in the absence of primary cardiac causes. The study enrolled 50 patients in whom serum cardiac troponin elevation occurred in the absence of any apparent cause within 3 days of symptoms onset. Fifty randomly selected, age- and sex-matched patients with stroke and normal serum cardiac troponin level served as controls. Right-side insula and inferior parietal lobe

strokes were shown to be associated with serum cardiac troponin elevation. Among patients with right middle cerebral artery infarction, the insula was involved in 88% of patients with and 33% of patients without serum cardiac troponin elevation [102]. In another study, Meyer *et al* prospectively studied the sympathetic function in 29 hemispheric stroke patients. Sympathetic activity was significantly higher in insular than in noninsular stroke ( $p < 0.05$ ), with concomitantly elevated cardiovascular parameters in patients with insular stroke [24]. Yet another study explored Holter monitoring for 24 h in 103 consecutive patients with first-ever acute stroke. When compared with all other stroke patients, subjects with right-sided insular damage showed significantly lower values of heart rate variability and more complex arrhythmias than any other localization ( $p < 0.05$ ) [14]. Insular infarction and nighttime blood pressure increase were significant and independent predictors of an unfavorable functional outcome [103]. Similar findings were reported by Tokgözoğlu *et al*, who demonstrated that stroke involving the insular region, particularly right-sided, leads to decreased heart rate variability and increased incidence of sudden death [104].

### Other hemispheric locations

The effect of parietal stroke on autonomic function was studied by Rincon *et al*, when epidemiological data of the Northern Manhattan Stroke Study (NOMAS) was analyzed [59]. The NOMAS is a population-based study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. In multivariate models, clinical diagnosis of left parietal lobe infarction was associated with cardiac death (adjusted OR = 4.45; 95% CI: 1.83–10.83). Furthermore, high risk of death after right-sided parietal lobe stroke, when the infarct size was taken into account, was observed. No association between frontal, temporal, or insular stroke and fatal cardiac events was seen, although the number of purely insular strokes was small. The study concluded that parietal lobe infarction is an independent predictor of long-term cardiac death or myocardial infarction in this population. Increased risk of cardiac events related to parietal stroke was observed only after a long-term follow-up [59]. The study further demonstrated that stroke involving the frontal lobe was a predictor of cardiac death. The ventromedial prefrontal cortex has significant modulating effects on cardiovascular responses to emotional stimuli (left prefrontal lesions result in dampened heart rate or blood pressure adjustment to visual emotional stimuli), whereas right prefrontal lesions mediate increase of heart rate and blood pressure responses [28].

## Modulation of autonomic nervous system: a new therapeutic target in cerebrovascular accidents

Activation of the parasympathetic nervous system has been successful in treatment of brain disorders such as depression and epilepsy [105–107]. This effect is mediated by antagonizing multiple pathological mechanisms [34]. Optimization of parasympathetic nervous system activation demonstrated neuroprotection in both preclinical models of cerebral ischemia and *in vitro* neuronal hypoxia [34]. In a rat model of transient focal cerebral ischemia, Ay *et al* demonstrated that vagus nerve stimulation (VNS) significantly decreased infarct size and neurological deficits 24 h after onset of ischemia [108]. VNS was found to reduce extracellular glutamate levels between 15 and 20 min after 5 min of experimental transient global ischemia [34,109]. Excitotoxicity occurring during ischemic brain injury could be antagonized by the reduction of glutamate levels. VNS may be neuroprotective by its anti-inflammatory effect and the mediation of norepinephrine release. Furthermore, parasympathetic activation was found to increase cerebral blood flow and improve neurogenesis [34]. In summary, activation of the parasympathetic nervous system has neuroprotective and anti-inflammatory effects on the CNS, as well as a modulatory effect on the cerebrovascular tone. These effects carry a promising therapeutic direction in prevention and treatment of autonomic dysfunction related to stroke.

## Conclusion

Autonomic dysfunction is common after vascular brain injury and may increase poststroke rate of morbidity and mortality. Although there is strong evidence suggesting the involvement of the insular cortex, particularly the right side, in increasing sympathetic tone and modulating autonomic function, studies also report an increased risk of cardiorespiratory dysfunction following frontal and parietal hemispheric stroke. The implementation of preventive and therapeutic strategies to antagonize the clinical manifestation of autonomic dysfunction may improve the outcome of stroke. This will rely on better understanding of the pathogenesis and molecular mechanism(s) of parasympathetic and sympathetic dysfunction after stroke. With the promising preclinical studies supporting the neuroprotective effect of VNS and its ability to antagonize multiple stroke pathologic mechanisms, autonomic nervous system modulation is emerging as a new therapeutic target for management and prevention of complications related to autonomic dysfunction related to stroke.

## Acknowledgements

The authors gratefully acknowledge the contributions by Jacqueline Grove, Medical Editor, Lehigh Valley Health Network, in the review and preparation of this manuscript.

## References

- Koennecke HC, Belz W, Berfelde D, Endres M, Fitzek S, Hamilton F, Kreitsch P, Mackert BM, Nabavi DG, Nolte CH, Pöhls W, Schmehl I, Schmitz B, von Brevern M, Walter G, Heuschmann PU. Berlin Stroke Register Investigators. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. *Neurology* 2011;77:965–72.
- McGovern PG, Burke GL, Sprafka JM, Xue S, Folsom AR, Blackburn H. Trends in mortality, morbidity, and risk factor levels for stroke from 1960 through 1990. the Minnesota Heart Survey. *JAMA* 1992;268:753–59.
- Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S. VISTA Investigators. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke* 2007;38:2295–302.
- Smith EE, Shobha N, Dai D, et al. A risk score for in-hospital death in patients admitted with ischemic or hemorrhagic stroke. *J Am Heart Assoc* 2013;2:e005207.
- Olson DM, Cox M, Pan W, Sacco RL, Fonarow GC, Zorowitz R, Labresh KA, Schwamm LH, Williams L, Goldstein LB, Bushnell CD, Peterson ED. Death and rehospitalization after transient ischemic attack or acute ischemic stroke: one-year outcomes from the adherence evaluation of acute ischemic stroke-longitudinal registry. *J Stroke Cerebrovasc Dis* 2012;22:e181–8.
- Greisenegger S, Zehetmayer S, Ferrari J, Lang W, Fizek J, Auff E, Lalouschek W, Serles W. Clinical predictors of death in young and middle-aged patients with ischemic stroke or transient ischemic attack: long-term results of the Vienna Stroke Registry: clinical predictors of ischemic stroke mortality in patients <60 years. *J Neurol* 2011;258:1105–13.
- Putala J, Curtze S, Hiltunen S, Tolppanen H, Kaste M, Tatlisumak T. Causes of death and predictors of 5-year mortality in young adults after first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke* 2009;40:2698–703.
- Dhamoon MS, Tai W, Boden-Albala B, Rundek T, Paik MC, Sacco RL, Elkind MS. Risk of myocardial infarction or vascular death after first ischemic stroke: the Northern Manhattan Study. *Stroke* 2007;38:1752–8.
- Kimura K, Minematsu K, Kazui S, Yamaguchi T. Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Mortality and cause of death after hospital discharge in 10,981 patients with ischemic stroke and transient ischemic attack. *Cerebrovasc Dis* 2005;19:171–8.
- Baptista MV, van Melle G, Bogousslavsky J. Death from ischemic stroke in the anterior circulation: the contralateral carotid matters. *Eur Neurol* 1999;41:15–19.
- Laowattana S, Zeger SL, Lima JA, Goodman SN, Wittstein IS, Oppenheimer SM. Left insular stroke is associated with adverse cardiac outcome. *Neurol* 2006;66:477–83.
- Norris JW, Froggatt GM, Hachinski VC. Cardiac arrhythmias in acute stroke. *Stroke* 1978;9:392–6.
- Engström G, Hedblad B, Juul-Möller S, Tydén P, Janzon L. Cardiac arrhythmias and stroke: increased risk in men with high frequency of atrial ectopic beats. *Stroke* 2000;31:2925–9.
- Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. *Stroke* 2004;35:2094–8.
- Daniele O, Caravaglios G, Fierro B, Natalè E. Stroke and cardiac arrhythmias. *J Stroke Cerebrovasc Dis* 2002;11:28–33.
- Kallmünzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, Schwab S, Köhrmann M. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors—a systematic, prospective analysis. *Stroke* 2012;43:2892–7.
- Orlandi G, Fanucchi S, Strata G, Pataleo L, Landucci Pellegrini L, Prontera C, Martini A, Murri L. Transient autonomic nervous system dysfunction during hyperacute stroke. *Acta Neurol Scand* 2000;102:317–21.
- Xiong L, Leung H, Chen XY, Han JH, Leung T, Soo Y, Wong E, Chan A, Lau A, Wong KS. Preliminary findings of the effects of autonomic dysfunction on functional outcome after acute ischemic stroke. *Clin Neurol Neurosurg* 2012;114:316–20.
- Ko SH, Song KH, Park SA, Kim SR, Cha BY, Son HY, Moon KW, Yoo KD, Park YM, Cho JH, Yoon KH, Ahn YB. Cardiovascular autonomic dysfunction predicts acute ischaemic stroke in patients with type 2 diabetes mellitus: a 7-year follow-up study. *Diabet Med* 2008;25:1171–7.
- Micieli G, Cavallini A. The autonomic nervous system and ischemic stroke: a reciprocal interdependence. *Clin Auton Res* 2008;18:308–17.
- Bassi A, Colivicchi F, Santini M, Caltagirone C. Cardiac autonomic dysfunction and functional outcome after ischaemic stroke. *Eur J Neurol* 2007;14:917–22.
- Colivicchi F, Bassi A, Santini M, Caltagirone C. Prognostic implications of right-sided insular damage, cardiac autonomic derangement, and arrhythmias after acute ischemic stroke. *Stroke* 2005;36:1710–15.
- Chkhikvishvili, TsSh; Antadze, ZI.; Sturua, NT.; Motsonelidze, MR. The pathogenetic and prognostic value of autonomic-hormonal shifts in ischemic stroke. *Zh Nevropatol Psikhiatr Im S S Korsakova* 1992;92:29–32.
- Meyer S, Strittmatter M, Fischer C, Georg T, Schmitz B. Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. *Neuroreport* 2004;15:357–61.
- Musulmanoglu L, Akyuz G, Aki S, Karsidaq S, Us O. Evaluation of autonomic nervous system functions in post-stroke patients. *Am J Phys Med Rehabil* 2002;81:721–25.
- Korpelainen JT, Sotaniemi KA, Myllylä VV. Autonomic nervous system disorders in stroke. *Clin Auton Res* 1999;9:325–33.
- Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc* 1993;68:988–1001.
- Hilz MJ, Schwab S. Stroke-induced sudden-autonomic death: areas of fatality beyond the insula. *Stroke* 2008;39:2421–22.
- Benarroch E, Biaggioni I. Central autonomic control Primer on the autonomic nervous system. San Diego, CA Academic Press 2012:9–12.
- Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol* 2003;13:500–05.
- Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu Rev Neurosci* 2002;25:433–69.
- Cechetto DF. Central representation of visceral function. *Fed Proc* 1987;46:17–23.

33. Verberne AJ, Owens NC. Cortical modulation of the cardiovascular system. *Prog Neurobiol* 1998;54:149–68.
34. Cheyuo C, Jacob A, Wu R, Zhou M, Coppa GF, Wang P. The parasympathetic nervous system in the quest for stroke therapeutics. *J Cereb Blood Flow Metab* 2011;31:1187–95.
35. Birder L, de Groat W, Mills I, Morrison J, Thor K, Drake M. Neural control of the lower urinary tract: peripheral and spinal mechanisms. *Neurorol Urodyn* 2010;29:128–39.
36. Sykora M, Diedler J, Turcani P, Hacke W, Steiner T. Baroreflex: a new therapeutic target in human stroke? *Stroke* 2009;40:e678–82.
37. Ropper AH, Samuels MA. Disorders of the autonomic nervous system, respiration, and swallowing. New York:McGraw-Hill;2013:505–12. In: Adam's and Victor's principles of neurology
38. Günther A, Salzmann I, Nowack S, Schwab M, Surber R, Hover H, Witte OW, Hoyer D. Heart rate variability – a potential early marker of sub-acute post-stroke infections. *Acta Neurol Scand* 2012;126:189–96.
39. He L, Li C, Luo Y, Dong W, Yang H. Clinical prognostic significance of heart abnormality and heart rate variability in patients with stroke. *Neurol Res* 2010;32:530–34.
40. Kwon DY, Lim HE, Park MH, Oh K, Yu SW, Park KW, Seo WK. Carotid atherosclerosis and heart rate variability in ischemic stroke. *Clin Auton Res* 2008;18:355–57.
41. Gujjar AR, Sathyaprabha TN, Nagaraja D, Thennarasu K, Pradhan N. Heart rate variability and outcome in acute severe stroke: role of power spectral analysis. *Neurocrit Care* 2004;1:347–53.
42. Katz-Leurer M, Shochina M. Heart rate variability (HRV) parameters correlate with motor impairment and aerobic capacity in stroke patients. *NeuroRehabilitation* 2005;20:91–5.
43. Nishioka Y, Sashika H, Andho N, Tochikubo O. Relation between 24-h heart rate variability and blood pressure fluctuation during exercise in stroke patients. *Circ J* 2005;69:717–21.
44. Arad M, Abboud S, Radai MM, Adunsky A. Heart rate variability parameters correlate with functional independence measures in ischemic stroke patients. *J Electrocardiol* 2002;35:243–46.
45. Robinson T, Potter J, Panerai R. Heart rate variability following ischemic stroke. *Stroke* 1999;30:2246–47.
46. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput* 2006;44:1031–51.
47. Dutsch M, Burger M, Dörfner C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. *Neurol* 2007;69:2249–55.
48. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Abnormal heart rate variability as a manifestation of autonomic dysfunction in hemispheric brain infarction. *Stroke* 1996;27:2059–63.
49. Chen CF, Lin HF, Lin RT, Yang YH, Lai CL. Relationship between ischemic stroke location and autonomic cardiac function. *J Clin Neurosci* 2013;20:406–09.
50. Korpelainen JT, Sotaniemi KA, Suominen K, Tolonen U, Myllylä VV. Cardiovascular autonomic reflexes in brain infarction. *Stroke* 1994;25:787–92.
51. Talman WT. Cardiovascular regulation and lesions of the central nervous system. *Ann Neurol* 1985;18:1–13.
52. Oppenheimer S. Cerebrogenic cardiac arrhythmias: cortical lateralization and clinical significance. *Clin Auton Res* 2006;16:6–11.
53. Oppenheimer SM, Cechetto DF, Hachinski VC. Cerebrogenic cardiac arrhythmias. Cerebral electrocardiographic influences and their role in sudden death. *Arch Neurol* 1990;47:513–19.
54. Robinson TG, Dawson SL, Eames PJ, Panerai RB, Potter JF. Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischemic stroke. *Stroke* 2003;34:705–12.
55. Mäkilä AM, Mäkilä TH, Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Heart rate dynamics predict poststroke mortality. *Neurol* 2004;62:1822–26.
56. Chen PL, Kuo TB, Yang CC. Parasympathetic activity correlates with early outcome in patients with large artery atherosclerotic stroke. *J Neurol Sci* 2012;314:57–61.
57. Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllylä VV. Abnormal heart rate variability reflecting autonomic dysfunction in brainstem infarction. *Acta Neurol Scand* 1996;94:337–42.
58. Taggart P, Critchley H, Lambiase PD. Heart-brain interactions in cardiac arrhythmia. *Heart* 2011;97:698–708.
59. Rincon F, Dhamoon M, Moon Y, Paik MC, Boden-Albala B, Homma S, Di Tullio MR, Sacco RL, Elkind MS. Stroke location and association with fatal cardiac outcomes: Northern Manhattan Study (NOMAS). *Stroke* 2008;39:2425–31.
60. Lavy S, Yaar I, Melamed E, Stern S. The effect of acute stroke on cardiac functions as observed in an intensive stroke care unit. *Stroke* 1974;5:775–80.
61. Goldstein DS. The electrocardiogram in stroke: relationship to pathophysiological type and comparison with prior tracings. *Stroke* 1979;10:253–59.
62. Morfís L, Schwartz RS, Poulos R, Howes LG. Blood pressure changes in acute cerebral infarction and hemorrhage. *Stroke* 1997;28:1401–05.
63. Zis P, Vemmos K, Spengos K, Manios E, Zis V, Dimopoulos MA, Zakopoulos N. Ambulatory blood pressure monitoring in acute stroke: pathophysiology of the time rate of blood pressure variation and association with the 1-year outcome. *Blood Press Monit* 2013;18:94–100.
64. Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, Minematsu K. Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. *Stroke* 2011;42:3511–17.
65. McLaren A, Kerr S, Allan L, Steen IN, Ballard C, Allen J, Murray A, Kenny RA. Autonomic function is impaired in elderly stroke survivors. *Stroke* 2005;36:1026–30.
66. Celovská D, Stasko J, Gonsorcik J, Diab A. The significance of baroreflex sensitivity in hypertensive subjects with stroke. *Physiol Res* 2010;59:537–43.
67. Eveson DJ, Robinson TG, Shah NS, Panerai RB, Paul SK, Potter JF. Abnormalities in cardiac baroreceptor sensitivity in acute ischaemic stroke patients are related to aortic stiffness. *Clin Sci (Lond)* 2005;108:441–47.
68. Robinson T, Potter J. Cardiopulmonary and arterial baroreflex-mediated control of forearm vasomotor tone is impaired after acute stroke. *Stroke* 1997;28:2357–62.
69. Sykora M, Diedler J, Rupp A, Turcani P, Steiner T. Impaired baroreceptor reflex sensitivity in acute stroke is associated with insular involvement, but not with carotid atherosclerosis. *Stroke* 2009;40:737–42.
70. Eames PJ, Blake MJ, Dawson SL, Panerai RB, Potter JF. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2002;72:467–72.
71. Nagai M, Hoshida S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. *J Am Soc Hypertens* 2010;4:174–82.
72. Sykora M, Diedler J, Rupp A, Turcani P, Rocco A, Steiner T.

- Impaired baroreflex sensitivity predicts outcome of acute intracerebral hemorrhage. *Crit Care Med* 2008;36:3074–79.
73. Robinson TG, James M, Youde J, Panerai R, Potter J. Cardiac baroreceptor sensitivity is impaired after acute stroke. *Stroke* 1997;28:1671–76.
  74. Naver HK, Blomstrand C, Wallin BG. Reduced heart rate variability after right-sided stroke. *Stroke* 1996;27:247–251.
  75. Riedl B, Beckmann T, Neundörfer B, Handwerker HO, Birklein F. Autonomic failure after stroke—is it indicative for pathophysiology of complex regional pain syndrome? *Acta Neurol Scand* 2001;103:27–34.
  76. Korpelainen JT, Sotaniemi KA, Myllylä VV. Asymmetric sweating in stroke: a prospective quantitative study of patients with hemispherical brain infarction. *Neurol* 1993;43:1211–14.
  77. Korpelainen JT, Sotaniemi KA, Myllylä VV. Hyperhidrosis as a reflection of autonomic failure in patients with acute hemispherical brain infarction. an evaporimetric study. *Stroke* 1992;23:1271–75.
  78. Labar DR, Mohr JP, Nichols FT 3rd, Tatemichi TK. Unilateral hyperhidrosis after cerebral infarction. *Neurol* 1988;38:1679–82.
  79. Fujita K, Yamamoto T, Kamezaki T, Matsumura A. Efficacy of keishibukuryogan, a traditional Japanese herbal medicine, in treating cold sensation and numbness after stroke: clinical improvement and skin temperature normalization in 22 stroke patients. *Neurol Med Chir (Tokyo)* 2010;50:1–5.
  80. Korpelainen JT, Sotaniemi KA, Myllylä VV. Asymmetrical skin temperature in ischemic stroke. *Stroke* 1995;26:1543–47.
  81. Herbaut AG, Cole JD, Sedgwick EM. A cerebral hemisphere influence on cutaneous vasomotor reflexes in humans. *J Neurol Neurosurg Psychiatry* 1990;53:118–20.
  82. Wanklyn P, Forster A, Young J, Mulley G. Prevalence and associated features of the cold hemiplegic arm. *Stroke* 1995;26:1867–70.
  83. Wanklyn P, Ilsley DW, Greenstein D, Hampton IF, Roper TA, Kester RC, Mulley GP. The cold hemiplegic arm. *Stroke* 1994;25:1765–70.
  84. Kucera P, Goldenberg Z, Kurca E. Sympathetic skin response: review of the method and its clinical use. *Bratisl Lek Listy* 2004;105:108–16.
  85. Zimmermann KP, Monga TN, Darouiche RO, Lawrence SA. Post-stroke autonomic nervous system function: palmar sympathetic skin responses thirty or more days after cerebrovascular accident. *Arch Phys Med Rehabil* 1995;76:250–56.
  86. Korpelainen JT, Tolonen U, Sotaniemi KA, Myllylä VV. Suppressed sympathetic skin response in brain infarction. *Stroke* 1993;24:1389–92.
  87. Linden D, Berlitz P. Sympathetic skin responses (SSRs) in monofocal brain lesions: topographical aspects of central sympathetic pathways. *Acta Neurol Scand* 1995;91:372–76.
  88. Han KS, Heo SH, Lee SJ, Jeon SH, Yoo KH. Comparison of urodynamics between ischemic and hemorrhagic stroke patients; can we suggest the category of urinary dysfunction in patients with cerebrovascular accident according to type of stroke? *Neurourol Urodyn* 2010;29:387–90.
  89. Chou YC, Jiang YH, Harnod T, Kuo HC. characteristics of neurogenic voiding dysfunction in cerebellar stroke: a cross-sectional, retrospective video urodynamic study. *Cerebellum* 2013;12:601–06.
  90. Brittain KR, Peet SM, Castleden CM. Stroke and incontinence. *Stroke* 1998;29:524–28.
  91. Williams MP, Srikanth V, Bird M, Thrift AG. Urinary symptoms and natural history of urinary continence after first-ever stroke—a longitudinal population-based study. *Age Ageing* 2012;41:371–76.
  92. Pettersen R, Wyller TB. Prognostic significance of micturition disturbances after acute stroke. *J Am Geriatr Soc* 2006;54:1878–84.
  93. Jung JH, Kam SC, Choi SM, Jae SU, Lee SH, Hyun JS. Sexual dysfunction in male stroke patients: correlation between brain lesions and sexual function. *Urol* 2008;71:99–103.
  94. Otegbayo JA, Talabi OA, Akere A, Owolabi MO, Owolabi LF, Oguntoye OO. Gastrointestinal complications in stroke survivors. *Trop Gastroenterol* 2006;27:127–30.
  95. Cheshire WP Jr, Saper CB. The insular cortex and cardiac response to stroke. *Neurol* 2006;66:1296–97.
  96. Fink JN, Selim MH, Kumar S, Voetsch B, Fong WC, Caplan LR. Insular cortex infarction in acute middle cerebral artery territory stroke: predictor of stroke severity and vascular lesion. *Arch Neurol* 2005;62:1081–85.
  97. Oppenheimer S. The insular cortex and the pathophysiology of stroke-induced cardiac changes. *Can J Neurol Sci* 1992;19:208–11.
  98. Macey PM, Wu P, Kumar R, Ogren JA, Richardson HL, Woo MA, Harper RM. Differential responses of the insular cortex gyri to autonomic challenges. *Auton Neurosci* 2012;168:72–81.
  99. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans. *Clin Auton Res* 1996;6:131–40.
  100. Butcher KS, Cechetto DF. Autonomic responses of the insular cortex in hypertensive and normotensive rats. *Am J Physiol* 1995;268(1 Pt 2):R214–22.
  101. Oppenheimer SM, Cechetto DF. Cardiac chronotropic organization of the rat insular cortex. *Brain Res* 1990;533:66–72.
  102. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG. Neuroanatomic correlates of stroke-related myocardial injury. *Neurol* 2006;66:1325–29.
  103. Sander D, Winbeck K, Klingelhöfer J, Etgen T, Conrad B. Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. *Neurol* 2001;57:833–38.
  104. Tokgözoğlu SL, Batur MK, Topçuoğlu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. *Stroke* 1999;30:1307–11.
  105. Thygesen KS, Sabers A. Promising effect of vagal stimulation in Danish patients with epilepsy. *Dan Med J* 2013;60:A4597.
  106. García-Navarrete E, Torres CV, Gallego I, Navas M, Pastor J, Sola RG. Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication. *Seizure* 2013;22:9–13.
  107. Henderson JM. Vagal nerve stimulation versus deep brain stimulation for treatment-resistant depression: show me the data. *Clin Neurosurg* 2007;54:88–90.
  108. Ay I, Lu J, Ay H, Gregory Sorensen A. Vagus nerve stimulation reduces infarct size in rat focal cerebral ischemia. *Neurosci Lett* 2009;459:147–151.
  109. Miyamoto O, Pang J, Sumitani K, Negi T, Hayashida Y, Itano T. Mechanisms of the anti-ischemic effect of vagus nerve stimulation in the gerbil hippocampus. *Neuroreport* 2003;14:1971–74.