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REVIEW

Autonomic Disturbances in Acute Cerebrovascular Disease

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Abstract Autonomic disturbances often occur in patients with acute cerebrovascular disease due to damage of the central autonomic network. We summarize the structures of the central autonomic network and the clinical tests used to evaluate the functions of the autonomic nervous system. We review the clinical and experimental findings as well as management strategies of post-stroke autonomic disturbances including electrocardiographic changes, cardiac arrhythmias, myocardial damage, thermoregulatory dysfunction, gastrointestinal dysfunction, urinary incontinence, sexual disorders, and hyperglycemia. The occurrence of autonomic disturbances has been associated with poor outcomes in stroke patients. Autonomic nervous system modulation appears to be an emerging therapeutic strategy for stroke management in addition to treatments for sensorimotor dysfunction.

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Introduction

Autonomic disturbances often occur in patients with acute cerebrovascular disease due to damage of the central autonomic network [1–4]. The central autonomic network consists of four hierarchal structures at the telencephalic, diencephalic, brainstem, and spinal levels [5]. Normal function of the autonomic nervous system (ANS) is critically dependent on the integrity of the autonomic network [6]. Brain injury in stroke, therefore, can cause various types of central autonomic disturbance depending upon the lesion site, particularly in the frontoparietal areas and brainstem [3]. Emphasis has mainly been laid on the recovery of motor functions; however, dysfunctions of the cardiovascular, gastrointestinal, thermoregulatory, sudomotor, or urinary system are common in stroke patients and can be detected clinically [2, 7, 8]. Emerging evidence has shown that autonomic disturbances after stroke are associated with unfavorable functional outcomes and increased mortality [2]. Thus, ANS modulation is emerging as a new therapeutic strategy for stroke management [9].

In this review, we summarize the anatomical structures and functional output of the central autonomic network as well as the clinical tests for evaluating autonomic function. In particular, we focus on the clinical manifestations and pathophysiological mechanisms of central autonomic disturbances associated with stroke.

Central Autonomic Network

The central autonomic network includes telencephalic, diencephalic, and brainstem structures (Fig. 1) [10].

Telencephalic Structures

The telencephalic structures consist of insular cortex, anterior cingulate cortex, and amygdala. The insular cortex is the primary interoceptive cortex and integrates visceral, pain, and temperature sensations from gustatory, visceral, muscle, and skin receptors *via* the thalamus [11–14]. It is also a visceromotor area, controlling both sympathetic and parasympathetic outputs, primarily *via* a relay in the lateral hypothalamic area [15]. The anterior cingulate cortex initiates autonomic responses related to motivation and goal-directed behavior. It is interconnected with the insular cortex and subdivided into ventral and dorsal regions, the activations of which vary according to experimental task and the associated sympathetic or parasympathetic response [16, 17]. The amygdala provides affective or emotional value to sensory stimuli and is involved in the autonomic and neuroendocrine response to stress. It has widespread connections with the hypothalamus and brainstem, particularly the periaqueductal gray and the medullary reticular formation [18]. *Via* these projections, the amygdala initiates autonomic and endocrine responses and motor activation that are critical for the expression of emotional responses, particularly the fear response [19].

Diencephalic Structures

The hypothalamus is the main anatomical component of diencephalic structures. The hypothalamus plays a central role in integrating the autonomic and endocrine responses necessary for homeostasis and adaptation [5]. It acts as a

Fig. 1 Diagram of the central autonomic network. Visceral information is relayed through the NTS and PBN to forebrain areas such as the hypothalamus, amygdala, thalamus, and insular cortex. The insular cortex has dense reciprocal connections with the ACC, lateral hypothalamic area, NTS, and PBN. These regions are also reciprocally connected. Infarction of the insular cortex may result in the loss of overall autonomic modulation and a decline in parasympathetic tone and baroreflex sensitivity, as well as a shift towards sympathetic dominance. ACC, anterior cingulate cortex; CeA, central amygdala; PBN, parabrachial nucleus; PAG, periaqueductal gray; NA, nucleus ambiguus; DMV, dorsal motor nucleus of the vagus; NTS, nucleus of the solitary tract; VLM, ventrolateral medulla.
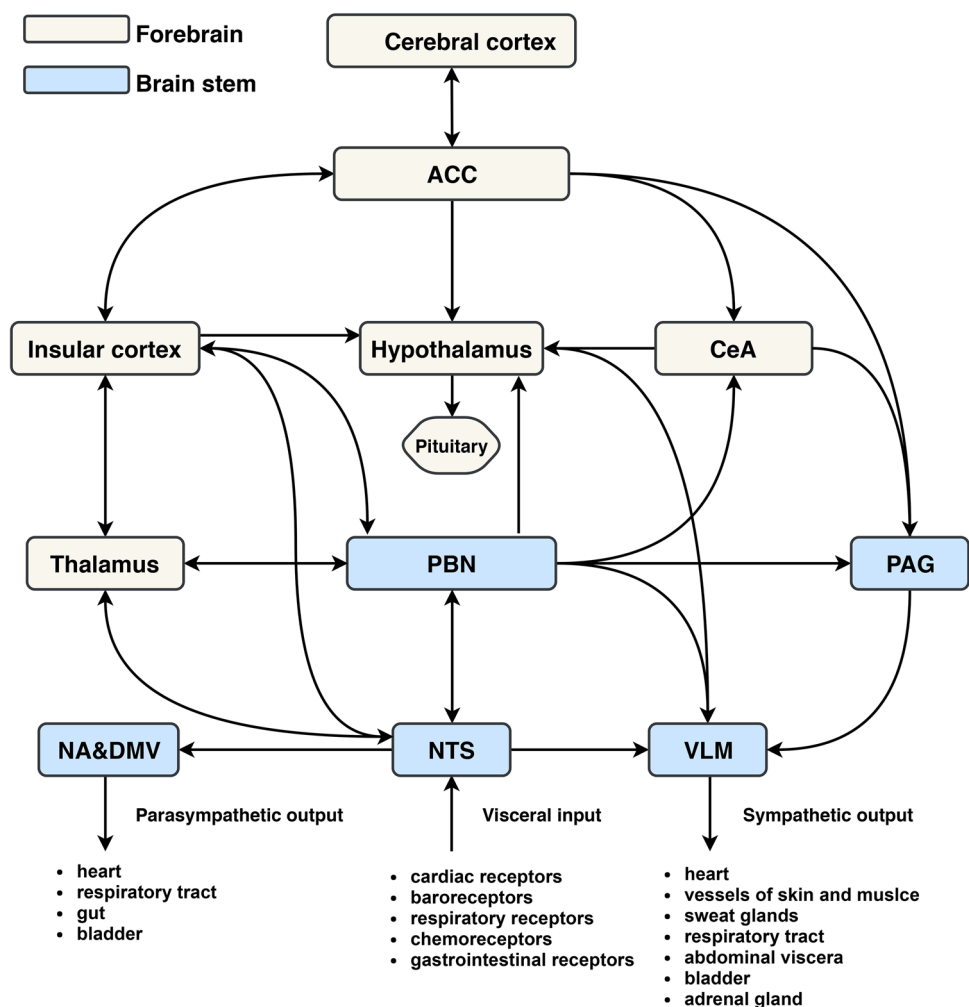
visceromotor pattern generator that initiates specific patterns of autonomic responses according to the stimulus, such as a hypoglycemia, body temperature, osmolarity, or external stressors [5]. The hypothalamus modulates not only stress, but also cerebral blood flow, food and sodium intake, glucose metabolism, and thermoregulation, as well as cardiovascular, renal, gastrointestinal, and respiratory functions [12].

Brainstem Structures

The brainstem structures consist of the periaqueductal gray (PAG), parabrachial nucleus (PBN), nucleus of the solitary tract (NTS), ventrolateral medulla (VLM), dorsal motor nucleus of the vagus (DMV), and nucleus ambiguus (NA). The PAG is the interface between the forebrain and the lower brainstem. It consists of different longitudinal columns, and, *via* their connections to the spinal cord, brainstem, and cortex, participates in the modulation of the cardiovascular, respiratory, thermoregulatory, urinary, reproductive, and pain-control systems [20]. The PBN is a major relay and coordinating center. It receives visceral, nociceptive, and thermoreceptive inputs from the spinal cord and conveys this information to the hypothalamus, amygdala, and thalamus [12]. The PBN also contains several subnuclei involved in taste, salivation, gastrointestinal activity, cardiovascular activity, respiration, osmoregulation, and thermoregulation [12]. The NTS is the first relay station of taste and visceral afferent information [5]. Different subnuclei of the NTS relay the information from baroreceptors and chemoreceptors, as well as cardiac, pulmonary, and gastrointestinal afferents, either directly or *via* the PBN, to the PAG, hypothalamus, thalamus (and then to the insular cortex), and amygdala [12, 21–23]. The VLM plays a critical role in regulating blood pressure [24]. Neurons in the rostral VLM include C1 adrenaline-synthesizing neurons and glutamatergic neurons that provide the major tonic excitatory input to sympathetic preganglionic neurons innervating resistance vessels of the muscles and visceral organs [21]. In addition, neurons in the caudal VLM include GABAergic and A1 noradrenergic neurons, which mainly mediate several cardiovascular reflexes and hypothalamic functions, respectively [6, 24]. The DMV contains most of the vagal preganglionic parasympathetic neurons; it receives inputs from the NTS and mediates all vagovagal reflexes controlling gastrointestinal motility and secretion [5]. The NA provides primary control of the heart *via* the cardiac ganglia, the neurons of which are excited by baroreceptor-sensitive NTS neurons and mediate the efferent cardioinhibitory component of the baroreflex [21].

Tests for Evaluation of the Autonomic Nervous System

Tilt Table Testing

Heart rate (HR) and blood pressure (BP) responses to orthostatic standing are well-established tests to assess parasympathetic and sympathetic nervous system activity, respectively [25]. A fall > 30 mmHg in systolic pressure and 15 mmHg in diastolic pressure when changing from the supine to the erect position is defined as abnormal [25]. It should be borne in mind that an abnormal fall in BP may also occur in patients taking antihypertensive drugs and other medications and in those with adrenal insufficiency and hypovolemia. It is suggested that medications should be stopped for five half-lives, and food, coffee, and nicotine should be avoided for 3 h before the test [26]. In resting healthy subjects, HR is determined by the predominantly vagal background autonomic activity. Upon standing, HR increases until it reaches a maximum at about the fifteenth heartbeat, after which it slows to a relatively stable rate at about the thirtieth beat. The 30:15 ratio (R–R interval at beat 30)/(R–R interval at beat 15) has been recommended as an index of cardiovagal function, the magnitude of which decreases with increasing age. In young adults, a ratio of < 1.04 is abnormal [25].

Valsalva Maneuver

The Valsalva maneuver is a useful screening test for evaluating the baroreflex [27]. During and after the maneuver, activations of baroreceptors in the thoracic viscera and arteries change the cardiac vagal efferent and sympathetic vasomotor activity [27]. Lesions of any of these autonomic pathways or of their central connections are likely to result in an abnormal HR response to the Valsalva maneuver. The patient breathes forcefully into a mouthpiece attached to a mercury manometer, maintaining an expiratory pressure of 40 mmHg for 10 or 15 s while an electrocardiographic (ECG) recording of the HR is made. In normal young adults, the ratio of the longest R–R interval to the shortest R–R interval during the maneuver is at least 1.45 [25]. A ratio lower than the age-matched control values usually indicates impaired ANS control of the heart and blood vessels, but low values may also be recorded in patients with heart and lung diseases [25].

Heart Rate Variation

Heart rate variation (HRV) is defined by the variation in heartbeat intervals or correspondingly in the instantaneous heart rate; it has been widely used to assess autonomic

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dysfunction following stroke [2, 4]. It shows the HR variation around the mean HR and reflects the balance between the sympathetic and parasympathetic nervous systems [26]. This test has become very popular for evaluating ANS function after stroke, because it is noninvasive, easy to perform, and has relatively good reproducibility [2, 28]. The assessment of HRV is generally based on time-domain or frequency-domain analysis. Time-domain analysis uses the mean HR, the standard deviation of normal-to-normal interbeat intervals (SDNN), and the root mean square of square sum of adjacent normal-to-normal interval difference (rMSSD) as the parameters. SDNN reflects overall HR variability, whereas rMSSD is correlated with vagal-mediated control [4]. Time-domain HRV analysis has the widest application in routine clinical evaluation and some of its indices have become well-documented, independent risk factors of cardiovascular events [29]. Frequency analysis splits a signal into its underlying frequencies. Parasympathetic modulation of HR is more pronounced in the frequency range 0.15 Hz–0.5 Hz (high-frequency range), while in the frequency ranging 0.04 Hz–0.15 Hz (low-frequency range), the HRV is controlled by a dual contribution of the sympathetic and parasympathetic nervous systems. The very low-frequency range corresponds to frequencies < 0.04 Hz and reflects the integrative effect of the various controllers, such as humoral effects [4]. The frequency-domain analysis of HRV is much better understood and is also mostly used for research purposes [30].

Baroreflex Sensitivity

The baroreflex is the major neural mechanism for BP control. A fall in BP leads to unloading of the baroreceptors in the carotid sinus and aortic arch, resulting in activation of sympathetic outflow and inhibition of cardiovagal neurons with a resultant increase in HR [26]. Baroreflex sensitivity (BRS) is quantified in milliseconds of R–R interval duration to each mmHg of arterial BP, with a normal value of ~ 15 ms/mmHg and a large interindividual difference [4]. Traditional approaches to test the BRS include pharmacological stimulation and neck suction. More recently, advances in beat-by-beat BP and HR monitoring methods have made it possible to estimate the BRS non-invasively from the R–R interval changes associated with spontaneous fluctuations in BP [27].

Thermoregulatory Sweat Test

The cholinergic part of the ANS can be assessed based on the reaction of sweat glands to various stimuli in the thermoregulatory sweat test [31]. The preganglionic centers that mediate the efferent sympathetic response include the hypothalamus, bulbospinal pathways, the intermediolateral cell column, and white rami [26]. In this test, sweat secretion after raising body temperature by 1 °C–1.4 °C (but below 38 °C) is measured. Various chemical powders that change color on exposure to moisture are used as indicators. The subject is placed in a sweat chamber with the air temperature at 45 °C–50 °C and humidity at 35%–50%. The peak response of sweat glands occurs after 35 min–45 min. Normal subjects should demonstrate generalized perspiration [27].

Plasma Catecholamines

The plasma catecholamine concentration has been accepted as an index of sympathetic activity in studies of cerebral vascular disorders [32, 33]. Noradrenaline is a neurotransmitter in the sympathetic nervous system and is released into the cleft of the nerve terminal-receptor site when the sympathetic nervous system is activated [32]. There is some "spillover" into the plasma on stimulation, so the plasma noradrenaline concentration is usually elevated if the sympathetic activity is increased [32]. However, venous plasma noradrenaline may not provide an accurate index of sympathetic activity as it reflects not only the vesicular release of noradrenaline from sympathetic nerve terminals, but also the effectiveness of junctional clearance. Clinicians should consider the effect of changes in organ/regional blood flow that would impact overall noradrenaline clearance. More recently, the regional noradrenaline spillover rate has permitted the assessment of noradrenaline release from specific organs. The "spillover" in steady-state conditions mirrors the secretion of noradrenaline from the sympathetic nerve terminals and is viewed as the gold standard for quantifying changes in sympathetic nerve activity, especially in human subjects [27].

Autonomic Disturbances After Stroke

Stroke can damage the anatomical structures of the central autonomic network, leading to autonomic disturbances (Fig. 2).

Cardiac Dysfunction

The manifestation of cardiac dysfunction following stroke includes ECG changes [34, 35], arrhythmias [36], and myocardial damage [3, 37]. Both experimental and clinical studies have indicated that hemispheric stroke involving the insular cortex or parietal lobe has particularly adverse effects in provoking cardiac consequences [38–40].

Fig. 2 Post-stroke autonomic disturbances caused by damage of the central autonomic network. **A** Brain structures of the central autonomic network. ACC, anterior cingulate cortex; PAG, periaqueductal gray; CeA, central amygdala; PBN, parabrachial nucleus; NTS, nucleus of the solitary tract; DMV, dorsal motor nucleus of the vagus; NA, nucleus ambiguus; VLM, ventrolateral medulla. **B** Specific autonomic disturbances correlate with damage of specific brain regions.
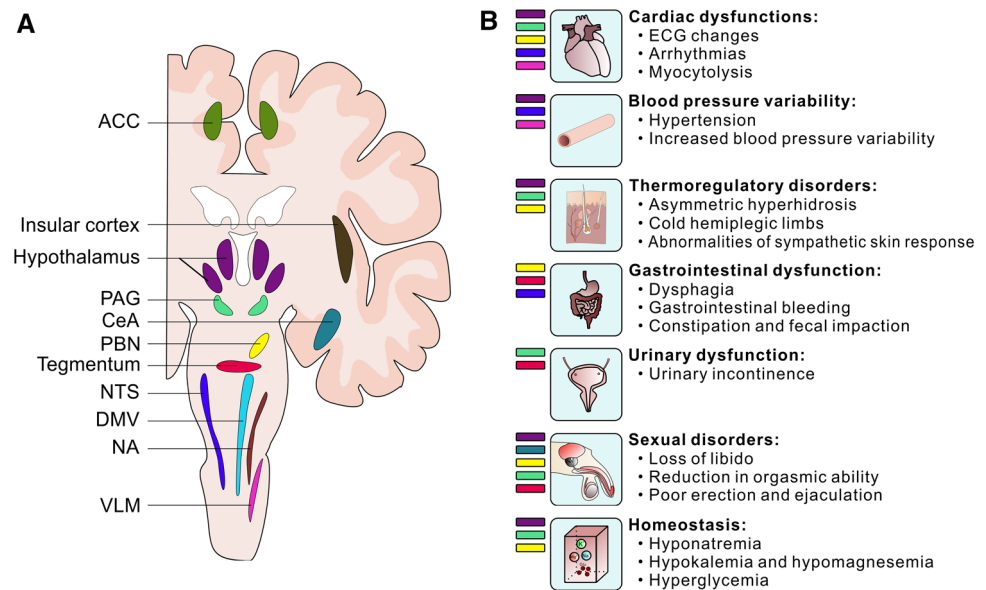
Damaged structures of the central autonomic network or connections could cause augmentation or inhibition of one or both divisions of the ANS, resulting in ECG changes without permanent effects on the myocardium. However, the catecholamine elevation associated with increased sympathetic tone could further cause ECG changes and myocardial damage. Cardiac dysfunction following stroke can be identified by ECG, echocardiography, cardiac enzyme levels, and coronary angiography [40].

ECG changes with considerable variation have been frequently reported in patients with acute stroke [34, 41–44]. The most common ECG abnormalities are prolonged QTc-intervals, ST-segment abnormalities, T-wave abnormalities, U-waves, and pathological Q waves (Table 1). Many factors including type of stroke and the localization of the lesion, pre-existing cardiac disorders, and electrolyte disorders may contribute to the variation of ECG abnormalities [34]. QTc prolongation seems to be the most common ECG abnormality reported in subarachnoid hemorrhage (SAH) patients, while patients with ischemic stroke have a higher frequency of T-wave abnormality [34]. Moreover, it seems that patients with history of cardiovascular disease and hypertension are more likely to have ECG alteration after stroke [34]. Although the initial cause of these changes is not fully clear, increased sympathetic output may be primarily responsible for the ischemic, arrhythmic, and repolarization changes of the ECG after stroke [45]. This hypothesis has been confirmed by clinical and experimental reports that insular cortex damage directly or indirectly affects cardiac function [42, 46, 47]. In contrast to ECG changes due to ischemic heart disease, stroke-induced ECG changes tend to appear later, reaching a maximum during the first few days after the onset of cerebrovascular events, and often revert to normal within 2 weeks [3].

Cardiac autonomic dysfunction after stroke may also manifest as various forms of cardiac arrhythmia [3]. The incidence of cardiac arrhythmias following stroke has been estimated to be between 17% and 80% [34, 41, 42, 45, 48, 49]. The wide spectrum of arrhythmias in stroke patients includes atrial fibrillation or atrial flutter, sinus tachycardia or sinus bradycardia, premature atrial or ventricular complexes, junctional rhythm, supraventricular tachycardia, asystole, ventricular tachycardia, torsade de pointes, and ventricular fibrillation [45, 50–52]. Such a high heterogeneity of ECG changes reported in different publications might be explained by the different durations and techniques of ECG recording, conflicting definitions of arrhythmias, inclusion or exclusion of patients with pre-existing cardiac diseases, and different locations and types of stroke [30].

In an earlier study of 150 acute stroke patients, Goldstein *et al.* assessed the incidence of ECG abnormalities as well as the new occurrence rate within 24 h of admission. Arrhythmias of any type occurred in 41/150 (27%) patients with acute stroke, and new arrhythmias occurred in 13/53 (25%) who had prior available tracings. Of all the arrhythmias, atrial fibrillation was the most common, occurring in 21/150 (14%) of patients. Sinus arrhythmia occurred in 10/150 (7%) and was a new finding in 2/53 (4%) of patients. Ventricular arrhythmias occurred in 7/150 (5%) of patients with acute stroke, and new ventricular arrhythmias were found in 4/53 (8%) of patients with prior available tracings [45].

Although the majority of cardiac arrhythmias are benign and do not need urgent therapeutic intervention, clinically

Table 1 ECG changes in stroke.

Authors	Study population	QTc-interval prolongation	ST-segment abnormalities	U-wave	Pathological Q wave	T-wave abnormalities	Arrhythmias
Togha et al. [34]	IS = 303, ICH = 41, SAH = 17	117 (32%)	84 (23%)	33 (9%)	57 (16%)	144 (40%)	98 (27%)
Ramani et al. [35]	IS = 53, ICH = 27, SAH = 19, CVT = 1	30 (30%)	25 (25%)	13 (13%)	6 (6%)	42 (42%)	30 (30%)
van Bree et al. [41]	ICH = 31	11 (36%)	5 (16%)	–	4 (13%)	5 (16%)	13 (42%)
Christensen et al. [42]	IS = 162, ICH = 17	11 (6%)	14 (8%)	–	–	38 (21%)	87 (49%)
Cruickshank et al. [44]	SAH = 40	22 (55%)	16 (40%)	13 (33%)	2 (5%)	29 (73%)	27 (68%)
Goldstein [45]	IS = 68, ICH = 16, SAH = 28, others = 38	18 (12%)	17 (11%)	14 (9%)	14 (9%)	32 (21%)	25 (17%)
Eisalo et al. [48]	SAH = 20	11 (55%)	11 (55%)	13 (65%)	–	9 (45%)	16 (80%)
Popescu et al. [49]	ICH = 120	60 (50%)	18 (15%)	–	–	–	40 (33%)
Arruda and de Lacerda [52]	ICH = 55, SAH = 15	45 (64%)	22 (31%)	8 (11%)	–	10 (14%)	14 (20%)
Dimant and Grob [54]	IS = 78, ICH = 12, SAH = 10	14 (14%)	44 (44%)	4 (4%)	5 (5%)	31 (31%)	34 (34%)

IS Ischemia stroke, ICH intracerebral hemorrhage, SAH subarachnoid hemorrhage, CVT cerebral venous thrombosis.

significant arrhythmias lead to high mortality and a poor functional outcome [51, 53]. Mortality among acute stroke patients with ventricular tachycardia, ventricular fibrillation, or asystole is significantly greater than that of patients without these ECG changes [45]. In a prospective study of SAH patients, clinically significant arrhythmias after SAH were defined as any rhythm disturbance other than sinus tachycardia, sinus bradycardia, and premature atrial and ventricular beats. In this cohort, 64% of the patients who experienced clinically significant arrhythmia were dead at 3 months [51]. Moreover, the incidence of sudden cardiac death in stroke patients ranges from 2% to 6%, and stroke-induced severe ventricular arrhythmias are responsible for the cardiac arrest [53]. Univariate logistic regression analysis has revealed that age and new injury severity score on admission are independent predictors of cardiac arrhythmia onset within the first 72 h after admission [53]. The risk for clinically significant cardiac arrhythmia after acute stroke is highest during the first 24 h and declines with time during the first 3 days. Therefore, close cardiac monitoring should be performed in the first 24 h, especially for aged patients with a severe neurological deficit [53].

In addition, post-stroke diffuse myocardial damage has been identified in both clinical and experimental studies [54, 55]. This is characterized by subendocardial hemorrhages, myofibrillar degeneration, lipofuscin pigment deposition in myofibrils, and lytic infiltration of a diffuse necrotic area in the heart [3]. This kind of injury was elucidated in an experimental study as myocytolysis, which has been associated with a catecholamine surge due to increased sympathetic hyperactivity [55]. Elevated levels of troponin (TnT), which is a highly sensitive and specific marker for myocardial damage, have been described in 9.6% of stroke patients [43]. A rise in TnT is significantly associated with a poor short-term outcome in stroke patients [43, 56].

Although there are currently no specific management guidelines for the post-stroke ECG changes, assessment of ECG and serum TnT levels is recommended for at least the first 24 h after stroke. This helps to screen for any significant arrhythmia and myocardial injury to prevent sudden cardiac death [57]. As ventricular tachycardia is the leading cause of stroke-induced cardiac arrest, several prospective trials have documented improved survival by applying prophylactic implantable cardioverter-defibrillator therapy in high-risk stroke patients with cardiac diseases and ventricular arrhythmia [53, 58]. Moreover, most of the stroke patients have coexisting electrolyte disturbances such as hypokalemia, which can lead to an increased risk of arrhythmias [59, 60]. Thus, intravenous infusion of potassium-free fluid should be avoided during the first day of stroke onset.

Blood Pressure Variability

The impairment of BP regulation resulting in its elevation and variation has frequently been reported in acute stroke

and is associated with an unfavorable outcome [61, 62]. The BP responds to stroke in a time-dependent manner. In a prospective study of 44 first-ever stroke patients, the incidence of high systolic and diastolic BP in patients with arrhythmia was 61.3%, 22.6% and 16.2% at the time of admission, 3 and 7 days after stroke onset, respectively. Similarly, in stroke patients without arrhythmia, an increased systolic and diastolic BP was recorded in 61.6%, 38.4% and 23.2% of patients at the time of admission, 3 and 7 days after stroke onset, respectively [63]. Sykora *et al.* investigated the BP and BRS of 45 patients with acute intracerebral hemorrhage (ICH) within 72 h from symptom onset. They found that systolic, diastolic, and mean beat-to-beat pressure variability were significantly increased compared with a control group. The BRS gain value, correlated with systolic, diastolic, and mean BP variability, has been proposed as an independent predictor of outcome at 10 days after ICH [64]. In another retrospective study, 98 aneurysmal SAH patients were divided into two groups: VS+ (developing vasospasm) and VS− (not developing vasospasm). Mean, systolic, and diastolic BP values progressed in both the VS− and VS+ cohorts over time. From days 1 to 8, the mean arterial BP increased by 28% in the VS+ group and 3.5% in the VS− group. An elevation of mean arterial BP by > 25% within the first week after SAH is associated with unfavorable outcomes [65].

The pathophysiology of post-stroke BP fluctuation may involve a mixture of various mechanisms, including pre-existing hypertension, activation of the renin–angiotensin–aldosterone axis, and mental stress. Autonomic dysfunction has also been suggested to be an important mechanism, particularly baroreflex dysfunction [9, 66]. The baroreceptors are located in the carotid arteries, cardiac chambers, and aortic arch, and are activated by beat-to-beat fluctuations in systemic BP. The baroreceptors relay information to the NTS and VLM, which is further processed in the insular cortex, medial prefrontal cortex, and hypothalamus. In normal healthy people, an elevated BP activates the baroreceptors and leads to an increase of vagal outflow and a decrease of sympathetic outflow, resulting in a decrease of vascular and cardiac tone [9]. In patients with stroke, an impaired central processing center could lead to baroreflex dysfunction, such as a hypertensive crisis or high BP variability. Of clinical importance, baroreflex impairment has been associated with a less favorable long-term outcome after acute ischemic stroke [61]. In addition, baroreflex failure has also been reported in patients with acute ICH, and this is correlated with beat-to-beat BP variability and independently predicts outcomes at 10 days after ICH [64].

Modulation of baroreflex sensitivity has been suggested to be a new therapeutic target in acute stroke [9].

Baroreflex sensitivity can be actively regulated by certain drugs, especially β-blockers [67, 68]. In a prospective study of 111 stroke patients, the use of β-blockers was independently associated with reduced stroke severity on presentation and better outcomes. Such a neuroprotective effect is most likely due to a sympatholytic effect associated with decreased thrombin, inflammation, and hemoglobin A_1C [69]. In addition, pre-treatment with β-blockers before the induction of experimental ischemia leads to a reduction in infarct volume by 40% [67].

Thermoregulatory Dysfunction

Sweating dysfunction after stroke is one of the most obvious and frequently-encountered symptoms of autonomic disturbance [70–72]. In hemiplegic patients, the paretic side of the body usually sweats more profusely and feels colder than the unaffected side [71]. In a prospective study, significant hyperhidrosis on the paretic side was observed in 55% of patients at baseline, and this phenomenon was more pronounced after exposure to heat for 5 min and 10 min [71]. Hyperhidrosis following stroke can occur at all sites (forehead, chest, forearm, hand, leg, and foot), but the face and arm seem to be the most common sites. Hyperhidrosis has been reported in patients with cortical and subcortical lesions, but the response seems to be equal in patients with frontal, parietal, and temporal lesions [71]. The pathogenesis of unilateral hyperhidrosis is still uncertain. The hyperhidrosis can be explained by failure of the suggested sympathoinhibitory pathway that controls sweating of the contralateral face and body. This putative pathway might originate from cortical areas and may follow the pyramidal tract, given that the degree of hyperhidrosis is associated with the severity of hemiparesis [71]. In addition, this hypothesis also explains some of the other manifestations of sympathetic hyperfunction in patients with stroke, such as cold extremities on the paretic side [73]. Although the phenomenon of hyperhidrosis has been reported to be associated with a severe neurological deficit and a poor prognosis [72], future investigation is needed to determine its clinical significance [70, 71].

Cold hemiplegic limbs have also been described in patient with stroke [3, 74, 75]. Although the symptoms can be present in the acute phase, the majority of patients recognize the coldness a few months after stroke onset [74, 75]. The explanation for this phenomenon hinges on the decreased cortical and subcortical inhibitory effect on vasomotor neurons, which subsequently increases the vasoconstrictor tone and reduces the cutaneous blood flow and skin temperature of hemiplegic limbs [3, 4].

The sympathetic skin response (SSR) is a simple method used in clinical practice to assess the reflex activity of the sympathetic pathway [76]. It is based on changes of skin conductance levels in response to various stimuli [76]. SSR

amplitude is significantly suppressed in hemispheric infarction compared with controls [77]. The abnormalities may be related to damage in the ascending and descending corticoreticular pathways or the cerebral cortex [3, 78].

Gastrointestinal Dysfunction

Gastrointestinal (GI) complications following stroke are common, with over half of stroke patients presenting with dysphagia, gastrointestinal bleeding, or fecal incontinence [79]. Although most of these manifestations are related to immobilization and the severity of stroke, impaired autonomic innervation of the gastrointestinal tract is a potential underlying mechanism [79]. The incidence of post-stroke dysphagia varies from 37% to 78%, depending on the screening techniques [80]. In a study of 40 post-stroke patients with dysphagia and swallowing difficulties, pharyngeal transit time was increased sixfold compared to controls [81]. The frequency of dysphagia was lowest in patients with unilateral ischemic hemispheric strokes, increased for those with bilateral hemispheric lesions, and greatest for patients with brainstem lesions [79]. In addition, ischemic stroke involving the middle cerebral artery or both hemispheres is associated with a higher incidence and severity of dysphagia. Dysphagia has emerged as an important cause of post-stroke malnutrition and pneumonia, as well as post-stroke mortality [80].

GI bleeding caused by "stress ulcers" mostly occurs 1 week after stroke onset and the incidence varies from 0.1% to 8% [82, 83]. There is a higher frequency of GI bleeding in elderly patients, with severe neurologic deficits, and using nonsteroidal anti-inflammatory drugs. Various studies have shown that multiple sites of brain activity, particularly in the hypothalamus and medulla, influence the secretion of gastric acid, which may be responsible for the GI bleeding after stroke [82–84].

The options available for treating post-stroke dysphagia are limited, but the utility of transcranial magnetic stimulation (TMS) has been evaluated in small studies. In a study of 26 monohemispheric ischemic stroke patients with post-stroke dysphagia, TMS significantly improved dysphagia and this was maintained over 2 months of follow-up [85]. Similar studies have found that anodal transcranial direct current stimulation of the motor cortex is able to improve the Dysphagia Outcome and Severity Scale scores [86, 87]. Considering the risk of aspiration, aggressive screening for post-stroke dysphagia is warranted [84]. The use of routine gastroprotective drugs as prophylaxis for GI bleeding in ischemic stroke patients is controversial, but intravenous administration of antiulcer agents (H2 receptor antagonists) for elderly and severe stroke patients is recommended by some international guidelines [88]. In addition, the selection of antiplatelet agents for secondary stroke prevention is important in order to minimize post-stroke GI bleeding [84]. While Cilostazol seems to be associated with fewer GI bleeds, both the combinations of aspirin-dipyridamole and aspirin-clopidrogrel can increase the risk of GI bleeding [89].

Urinary Incontinence

Urinary incontinence (UI) is a common sequela of acute stroke, affecting more than a third of stroke patients admitted to hospital, with up to a quarter of these patients remaining incontinent at 1 year [90]. It is an involuntary leakage of urine accompanied or immediately preceded by urgency, and urodynamic assessment often reveals uninhibited detrusor contraction [90]. Brittain *et al.* analyzed the prevalence of UI in stroke patients based on nine hospital-based studies published between 1985 and 1997. They found that the incidence of UI at hospital admission for stroke ranges from 32% to 79% [91]. Kolominsky-Rabas *et al.* reported an incidence of UI of 35% at 7 days following stroke [92]. Based on data from the UK National Sentinel Stroke Audit between 1998 and 2004, Wilson *et al.* identified UI rates of 39%–44% at 1 week after stroke [93]. The variation of post-stroke UI incidence among these studies may be due to different definitions of UI, failure to account for the presence of premorbid incontinence, and the different time points of UI assessment.

The regulation of micturition requires connections between many areas in the brain and spinal cord that involve the sympathetic, parasympathetic, and somatic systems [94]. These mechanisms control smooth and striated muscle activity of the urinary bladder, the bladder neck, the urethra, and the urethral sphincter to allow bladder filling and voiding to take place in a coordinated manner. Injury of the suprapontine pathway as a result of a stroke lesion could remove the tonic inhibitory control over the pontine micturition center, resulting in decreased bladder capacity and detrusor overactivity [90, 94].

Current therapeutic options for post-stroke UI include bladder retraining and the use of anticholinergic medications. In addition, environmental and lifestyle interventions need to be considered, such as easy access to the toilet, use of hand-held urinals, access to a call bell, reducing caffeine intake, and changes to medications that exacerbate incontinence [90]. It is important for clinicians to formulate an accurate differential diagnosis of functional incontinence caused by stroke from the overflow incontinence, because the treatments are completely different.

Sexual Disorders

Sexual dysfunction in stroke patients is complex and etiologically multifactorial, including a variety of physical and psychosocial factors [95]. Previous studies have

reported that the most common post-stroke sexual dysfunctions manifest as (1) a decline in libido and coital frequency, as well as reduction in vaginal lubrication and orgasmic ability in female patients; and (2) poor or absent erection and ejaculation in male patients [95, 96]. Studies in animals have shown that the media preoptic area, amygdala, paraventricular nucleus, periaqueductal gray, and ventral tegmentum are important integration centers for sexual function and penile erection [97]. Cerebrovascular accidents involving these regions are often associated with erectile dysfunction [97]. In addition to neurologic and cognitive deficits, the quality of sexual life may be impaired due to comorbidity, medication, fear of a new stroke, rejection by the spouse, loss of self-esteem, incontinence, and other urinary/sexual disturbances [3].

Hyperglycemia

Hyperglycemia occurs in 60% of acute stroke patients, of whom 12%–53% did not have the prior diagnosis of diabetes [98]. In non-diabetic stroke patients, the median blood glucose level rises from 5.9 mmol/L at 2.5 h to 6.2 mmol/L at 6 h post-stroke [99]. Two underlying mechanisms contribute to hyperglycemia after stroke: (1) the increased sympathetic activation results in increased output of glucose from the liver and stimulation of glucagon from the pancreas with insulin inhibition [100]; and (2) hypothalamic dysfunction induced by stroke can increase the secretion of cortisone and noradrenaline, which may contribute to the development of insulin resistance [101].

Hyperglycemia in both diabetic and non-diabetic patients has been linked to a poor prognosis both in terms of mortality and functional recovery, independent of the patient's age, severity of the condition, or stroke type [102, 103]. Hyperglycemia facilitates the development of cellular acidosis in the ischemic penumbra and results in a greater infarct volume, thus promoting the recruitment of potentially salvageable neurons into the infarction [98]. In addition, hyperglycemia is associated with inflammation and oxidative stress as well as increased expression of matrix metalloproteinase (MMP) 9 and MMP-2 [98], which may promote the hemorrhagic transformation of infracted brain tissue. A higher risk of hemorrhagic transformation has been reported in stroke patients with serum glucose levels > 8.4 mmol/L [104]. Substantial reductions in plasma glucose concentrations can be achieved using intensive intravenous insulin. Although it remains controversial, most clinicians consider initiating insulin treatment among stroke patients with a blood glucose level > 11.10 mmol/L [105]. Close monitoring of glucose concentrations and adjusting insulin doses accordingly are strongly recommended to avoid hypoglycemia [105].

Prospective and Conclusions

Since the central autonomic network damage is almost inevitable in acute cerebrovascular disease, autonomic disturbances are important consequences of stroke. Emerging evidence has demonstrated the association of post-stroke autonomic complications with poor outcomes. However, the previous preclinical and clinical publications are mainly observational. Future studies are warranted to better understand the underlying molecular mechanism(s) involved in sympathetic and parasympathetic dysfunction following stroke.

In addition, there is a need to establish new testing modalities for evaluating autonomic disturbances in the setting of acute cerebrovascular events, particularly in aged patients with severe neurological deficits. Given that autonomic functions can be influenced by medication, hospital stress, lifestyle, and, most importantly, pre-existing comorbidity including diabetes, hypertension, and cardiovascular disease, the results of tests should be interpreted carefully in accordance with the clinical manifestations.

It has been reported that optimization of parasympathetic nervous system activation is neuroprotective in both preclinical models of cerebral ischemia and in vitro neuronal hypoxia [106–108]. In a rat model of transient focal cerebral ischemia, Ay *et al.* demonstrated that vagus nerve stimulation (VNS) significantly decreases infarct size and neurological deficits 24 h after onset of ischemia [109]. The mechanism of the anti-ischemic effect of VNS was suggested to be a reduction in extracellular glutamate level after brain ischemia [110, 111]. Modulation of the ANS has been suggested to be a promising therapeutic direction in the prevention and treatment of autonomic dysfunction related to stroke.

Currently, specific guidelines for the management of post-stroke autonomic disturbances are lacking, even though life-threatening ventricular arrhythmias can occur after stroke. We stress the importance of treating stroke-induced arrhythmias, cardiac injury, and hyperglycemia in a timely manner by clinicians who are experienced in the diagnosis and treatment of these situations. The development of therapeutic strategies targeting the autonomic nervous system dysfunction will improve the overall outcome for stroke patients.

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