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REVIEW ARTICLE

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The autonomic nervous system and ischemic stroke: a reciprocal interdependence

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Abstract Signs and symptoms of autonomic nervous system (ANS) dysfunction are frequently reported after ischemic or haemorrhagic stroke and in many cases they exhibit peculiar patterns in relationship with the site and the extension of brain lesion. However if an ANS disorder can cause or predispose to a stroke is far from being correctly known. Evidences in favor of a pathogenetic mechanism of an ANS dysfunction are reported for myocardial infarction and such data are likely to be appropriate also for atherothrombotic type of ischemic stroke. On the other hand, it is well known that many risk factors for this pathology are strongly correlated with an altered functioning of ANS so that a reciprocal interdependence between ANS and stroke can be hypothesized. This review points to evidence the possible relationship existing between these two conditions and suggests a quite different diagnostic and therapeutic approach to both on the basis of their pathogenetic mechanisms.

Key words autonomic nervous system · stroke · atherosclerosis · circadian rhythms · cardiovascular dysfunction

Introduction

Cerebrovascular ischemia could be considered a dynamic process in which acute risk factors are superimposed to chronic risk factors to precipitate the ischemic event.

The ANS may contribute to the substrate of risk in the pre-pathological state or play a part in determining the precipitating factor(s) of the acute phase of stroke. Equally, in both the acute and chronic phases of stroke, ANS dysfunction may determine comorbid conditions or clinical complications with a negative prognostic significance. This dual role of the ANS in cerebrovascular disease pathogenesis and in the onset of the clinical manifestations is intriguing, linking both risk factors and clinical features of stroke with ANS dysfunction (acute and/or chronic) capable of modulating the interactions between external and internal environmental factors and of provoking the onset and progression of the disease.

We will discuss the role of ANS functioning in determining the progression of atherosclerosis and/or its risk factors, as well as in inducing particular complications in the acute and/or chronic phase after a cerebrovascular accident has occurred, in order to

contribute to a better knowledge of ANS functioning in physiology and pathology and to constitute a premise for a better therapeutic approach to prevention (primary and secondary) of factors precipitating the events leading to stroke in clinical practice.

From ANS to cerebral ischemia

Atherosclerosis is the leading cause of ischemic stroke and it is widely recognized to be a disease of chronic inflammation. Recent evidence reveals that the immune system is under the direct control of the vagus nerve via the "cholinergic anti-inflammatory pathways" [25, 58]. Stimulation of vagus nerve activity induces a significant decrease in cytokine levels in animal models; conversely, vagotomy is able to enhance the cytokine response to invasive stimuli. The CARDIA study [72] detected, in a large sample of healthy young adult, an inverse relationship between RR internal variability and inflammatory markers. Elevated intracellular expression of proinflammatory cytokines has been detected in patients with carotid atherosclerosis (particularly with complicated plaques) and an increase in peripheral blood intracellular cytokines has been suggested to be a warning signal of plaque progression [61, 62]. Moreover intima-medial thickness, a marker of subclinical atherosclerosis, and bilateral carotid atherosclerosis are associated with reduced baroreflex sensitivity [24, 55]. These data support the hypothesis that reduced descending vagal anti-inflammatory signals can allow cytokine overproduction in humans contributing to the growth of the atherosclerotic plaque.

Diet, age, gender, family history, stress, lifestyle, smoking, diabetes, dyslipidemias and hypertension represent well-recognized risk factors for atherosclerosis. An autonomic dysfunction with a sympathovagal balance shifted towards a chronic sympathetic state could be the final pathway triggering the common atherosclerotic process. Early diabetic autonomic neuropathy is characterized by a parasympathetic impairment.

A sympathetic hyperactivity has been suggested to play a central role in the pathogenesis of hypertension [44, 59] and hypertension is a well-recognized major risk factor for stroke documented in about the 80% of ischemic stroke patients. In healthy people the 24-hour profile of blood pressure (BP) is characterized by a fairly smooth profile during the daytime and by a significant decline of BP value during night sleep. In hypertensive patients a circadian pattern of BP is usually maintained, but these subjects show an upward shift of the BP curve throughout the 24-hour period compared with normotensive subjects, and the rhythm amplitude may be increased [52]. The Ohasama Study [35], a long-term prospective cohort study with ambulatory BP monitoring in the general population of a rural Japanese community, demonstrated a significant increase in cardiovascular mortality with an increase in BP variability and a decrease in heart rate (HR) variability. However the PAMELA study, a long term study on the prognostic value of BP variability in the general population in Italy, failed to detect any relationship between the risk of death and 24-hour, day, and night BP SDs suggesting that short-term erratic components of BP variability could play a prognostic role, with their increase being correlated with an increased cardiovascular risk [45]. Metoki et al. [50] followed the incidence of stroke in 1,430 subjects aged ≥40 years who have been participating in the Ohasama Study, for an average of 10.4 years. They found no significant association between total stroke risk and the nocturnal decline in BP or the morning pressure surge. However the ischemic stroke risk was significantly higher in subjects with a <10% nocturnal decline in BP whereas the intracerebral haemorrhage risk was associated with a large morning pressure surge and nocturnal decline in BP.

Moreover hypertension could also play a role in the development of atherosclerotic disease. Although hypertension has been reported to be either associated or not associated with carotid atherosclerosis [12, 60], the daytime systolic BP variability has been found by Sander et al. [67], in a 3-year follow-up study, to be a strong predictor of early carotid atherosclerosis progression measured with B-mode ultrasonography. The progression of intima-media thickness (IMT) of the common carotid artery was significantly greater in patients with increased systolic BP variability (0.11 mm/y vs. 0.05 mm/y; $P < 0.005$) even after the adjustment for other predictors for the progression of IMT (age, pack/years of smoking, diabetes, systolic and diastolic BP, heart rate, heart rate variability, cholesterol, triglycerides, circadian BP variation and prevalent ischemic heart disease). Both an additional 0.005–0.012 mm/y progression of IMT for every mm Hg increase in BP variability and a significantly increased relative risk of the development of early atherosclerosis with the raised daytime systolic BP variability greater than 15 mm Hg have been detected. Data on BP, even if not completely conclusive, strongly underline the importance of a strictly BP control also in healthy subjects, with target BP values <140/85 mmHg in non-diabetic and <130/80 mmHg in diabetic subjects in order to correctly prevent cerebrovascular accidents. At present it is not clear if specific classes of hypertensive agents could play a different role in the primary prevention of ischemic stroke.

Smoking induces an increase in sympathetic activity and a whole body increase in sympathetic state with increasing age has been reported by Seals and Esler [69]. Patients with fobic anxiety, a behavioral stress state, have low HR variability and a higher rate of sudden cardiac death and coronary artery disease than controls. The benefit of exercise in the prevention of cardio and cerebrovascular disease could at least partially relate to the reduction of chronic psychological stress. In fact the exercise is able to potentiate vagal input and to increase HR variability [48].

It is also well known that sleep-related breathing disorders, particularly obstructive sleep apnea syndrome (OSAS), represent an important risk factor for stroke. Yaggi et al. [81], in a large observational cohort study, demonstrated that OSAS is associated with an increased incidence of stroke and death (adjusted hazard ratio: 1.97, 95% CI: 1.12–3.48, $P < 0.01$). The severity of sleep apnea was significantly associated with an increased risk of the end-point ($P < 0.005$) and this was confirmed also in the elderly population (hazard ratio: 2.52, 95% CI: 1.04–6.10, $P < 0.04$). Sleep state has a profound effect on cerebral haemodinamycs. Several studies using various methods (transcranial Doppler ultrasonography, ^{133}Xe inhalation, single-photon emission CT) have detected 5–28% reduction in cerebral blood flow during non-rapid eye movement (REM) sleep and a 4–41% increase in REM sleep compared with wakefulness in normal persons. These changes induced parallel variations in the brain metabolic state and oxygen consumption and are independent of extracerebral hemodynamics factors. A significant regional cerebral blood flow decrease, particularly evident in brain stem and cerebellum regions, has been detected in patients with obstructive sleep apnea during non-REM sleep. During apneic episodes cerebral perfusion pressure decreased by about 11.2 ± 7.8 mmHg and this decrement is related to the duration of apneas and the degree of oxygen desaturation. Moreover these episodes of cerebral underperfusion are associated with cerebral oxygen desaturation on near-red spectroscopy suggesting cerebral ischemia during apneas. Abnormalities of cerebral vascular response to hypercapnia have been found also during wakefulness suggesting an impaired cerebral autoregulation in these patients also out of the apneic episodes. At the end platelet aggregation, both spontaneous and after activation and fibrinogen levels are significantly enhanced in patients with severe obstructive sleep apnea during the night [51]. The combination of cerebral hypoperfusion and hypercoagulability could represent the main pathophysiological mechanism for increasing risk of stroke in this population and the autonomic nervous system plays a key role in mediating cardiovascular changes during sleep apnea. OSAS may have direct and deleterious effects on cardiovascular function and structure. In particular, it can contribute to the state of chronic sympathetic hyperactivity. Nocturnal apneic episodes are characterized by extreme levels of sympathetic nervous system stimulation. Narkiewicz et al. [54] suggested that, over time, this might be generalized into an ongoing, daytime sympathetic overactivity. This sympathostimulating effect is independent of body weight but contributes to the overall sympathetic hyperactivity of obesity [27]. The studies on parasympathetic nervous system (PNS) activity of OSAS are very scant. The high frequency (HF) component is decreased in OSAS and the autonomic nerve balance is significantly declined showing sympathetic nerve dominance. In a recent preliminary study on the influence of OSAS upon cumulative PNS activity, a negative correlation has been recognized between cumulative PNS activity and OSAS severity [75]. Therapy with continuous positive airway pressure (CPAP) was associated with significant benefits to cardiovascular morbidity and mortality but there is a clear need of further studies evaluating the impact of CPAP therapy on the primary prevention of ischemic stroke.

From ANS dysfunction to cerebral ischemia onset

In this condition of chronic sympathetic hyperactivity due to the failure of carotid baroreceptor and chemoreceptor, the occurrence of exogenous factors (infections, surgery, cervical trauma and manipulation, pregnancy and the postpartum state, medications, physical or mental stress, and sudden changes in posture) can temporarily potentiate the risk of ischemic stroke and can determine the onset of acute stroke. The ANS mediates this interaction [21, 38] with a further increase of the sympathetic tone and with the impairment of carotid baroreceptors and chemoreceptors. The increase of sympathetic tone enhances internal triggers like vasoconstriction, increasing platelet aggregation, decreasing fibrinolysis, and increasing pulse rate and BP. The baro- and chemoreceptors impairment prevents an accurate detection of physical and chemical parameters with a misperception of hypoxia and/or hypotension which compromises cerebral perfusion [19]. In this regard alterations of the circadian pattern of BP and sleep-related breathing disorders could play a crucial role also in triggering the onset of ischemic stroke.

A circadian variation in the onset of cardiovascular events has been observed in various studies, with the highest incidence reported in the morning [6, 52, 53, 74, 80]. Data on ventricular arrhythmias [13, 14] and

myocardial ischemia (MI) [14, 39] seem to point to the existence of an endogenous circadian pattern of occurrence, which is independent of external triggers. In a large unselected population [6], ischemic stroke onset was more frequent in the morning, during the first few hours of diurnal activity, with a second peak recorded in the evening and minimum occurrence during the night. All the subgroups of patients with ischemic stroke (atherothrombotic, lacunar, cardioembolic, of undetermined cause, or with different location and/or extension), stratified according to risk factors, clinical variables, and putative cause of stroke, showed the same pattern of occurrence. Although the only significant common risk factor was hypertension, patients with and without hypertension had the same chronobiological pattern of stroke onset suggesting a primary role of BP circadian variability in triggering ischemic stroke onset. The absence of a normal drop in systolic BP from day to night (patients who show this are called "non-dippers") is predictive of heart failure, stroke, and MI, as well as sudden death in elderly patients with hypertension [73]. The increase in physical activity upon arising is regarded as the major determinant of the morning surge in BP [34], as also demonstrated by the stability of BP and HR before and after awakening in subjects who remained supine [74]. One may speculate that antihypertensive agents focused to control BP morning rise might be more efficacious in preventing ischemic stroke onset, but confirmatory clinical trials are needed.

It is likely, both in the presence and absence of hypertension, that sympathetic activation contributes to determining stroke onset also by interfering with the circadian organization, since the 24-hour variations in vascular events correspond to physiological BP variations and to oscillations of genes involved in haemostasis [29]. The biological clock in mammals is located centrally in the suprachiasmatic nucleus (SCN) [64]. Although the SCN is the master regulator, it is now accepted that there are molecular clocks in most peripheral tissues, capable of entrained and autonomous functions [68]. Clocks potentially relevant to cardiovascular function have been identified in the aorta [49], liver, kidney, and heart [16]. The clock may influence the vascular response to stress indirectly, by controlling the underlying rhythm of BP on which asynchronous cues are imposed, but also directly by modulating pressor response, irrespective of timing. Both effects reflect the influence of the clock on sympathoadrenal activation, which is observable in the integrated response of arousal and many of its elements, such as assumption of the orthostatic posture, exercise, and emotional stress [15]. An anatomical connection, via sympathetic nerves, seems to exist between the SCN and the adrenal gland, as demonstrated by transneural virus tracing [5] and light-induced *per1* induction of the adrenal gland [31]. A recent study demonstrates that genes (BMAL1, CLOCK and NPAS2) which subserve core functions in the molecular clock differentially regulate enzymes that play an important role in the synthesis and disposition of catecholamines. Disruption or deletion of clock genes causes alterations in BP pattern, plasma norepinephrine and epinephrine, their circadian variations, and also their response to immobilization stress [15]. Clock-dependent effects on BP, as well as on haemostatic factors such as plasminogen activator inhibitor (PAI-1) [3] could be able to determine the diurnal incidence in cardiovascular events.

Concerning the role of sleep-related breathing disorders in triggering the onset of cerebral ischemia, it is still unclear. Kirkham et al. [36] indicated nocturnal hypoxia as predictor of future cerebrovascular events in sickle-cell disease and Kario et al. [33] reported a case of a nocturnal onset ischemic stroke directly provoked by sleep-disordered breathing advanced with congestive heart failure.

ANS dysfunction and ischemic stroke prognosis

It is now well known that acute cerebral ischemia can deeply affect autonomic nervous system activity and this dysregulation may negatively influence the outcome.

In a recent study conducted with 184 patients with ischemic stroke, circadian (cycle of 20–28 hours), ultradian (shorter than 20 hours) and infradian (longer than 28 hours) rhythms of rectal and wrist temperature were investigated in the first 24 hours after onset of symptoms [76]. On the basis of the detection of a circadian rhythm of rectal temperature (RT) and wrist motor activity (WMA) patients were subdivided into three groups: normal (power spectra showing prominent circadian rhythms for RT and WMA), separate (power spectra showing prominent circadian rhythm for either RT or WMA), and aberration (power spectra showing prominent aberrant rhythms, ultradian or infradian, for both RT and WMA). Sixteen (32.0%), 20 (40.0%), and 14 (28.0%) of patients were classified, using the maximum entropy method (MEM), in the normal, separate, and aberrant groups of RT and WMA power spectra. The aberrant group consisted mainly of patients with cardioembolism and only a few with small-vessel occlusion and large artery atherosclerosis, in comparison with the separate group. Prognosis was significantly poorer in the aberrant group compared to the normal and separate groups, and the modified Rankin Scale was significantly worse in the aberrant group than the normal and separate groups.

As previously reported, a disruption of the normal pattern of circadian BP variation could trigger stroke onset but a loss/reduction in the nocturnal BP decline is also detectable in acute stroke patients. This occurs only in the presence of multiple lacunar infarction involving deep and specific regions (striatum, diencephalon, frontal operculum, cingulated gyrus and their connections), thalamic haemorrhage, pontine tegmentum infarction and pontine haemorrhage, suggesting that in the acute phase a direct injury of the central autonomic network underlies this BP derangement [82, 83]. Moreover an increase in BP variability is also reported in acute stroke patients and it is probably due to an impairment of cardiac baroreceptor sensitivity associated with a cerebral cortical dysfunction. In fact the pulse interval variability is not decreased. A significant reduction in cardiac baroreflex sensitivity after acute stroke has been demonstrated and it could be an important factor contributing to BP variability after stroke. Using lower body negative pressure to assess the integrity of "low-pressure" cardiopulmonary- and "high-pressure" arterial baroreceptor-derived responses, abnormalities of vasomotor tone after acute stroke in response to both receptors have been found [65]. These altered responses persist in the subacute period and could be related to direct, stroke-related damage of the central connections of the cardiovascular reflex arcs or to impaired vasoconstriction in skeletal muscle. The increase in BP variability could have an important effect on central blood flow and on the potential viability of the ischemic penumbra. A deleterious effect of an increased BP variability on the ischemic penumbra could explain the related poor outcome but available data are still inconclusive and controversial. For example Pandian et al. [57] investigated the circadian BP variation in 173 stroke patients enrolled within 24-hours of stroke, failed to find a significant correlation between circadian BP patterns and outcome.

However, it is well defined that a correct BP management in the acute phase of stroke can positively influence the outcome and observational studies suggest that approximately 75% of patients with ischemic stroke have elevated BP readings within 24–48 hours of onset. Blood pressure is generally higher in patients with intracerebral haemorrhage than in those with ischemic stroke. The natural pattern is for BP to begin falling within hours of stroke onset, and subsequently to reach a stable level over the first weeks after stroke. In patients with mild-to-moderate cerebral infarction, BP stabilizes 24 hours after admission, and this level remains similar to those recorded 4 days or 3 months after admission [9]. In severe stroke the decrease in BP is slower; in fact, BP values throughout the first seven days are higher than those monitored 3 months later. It is also possible to observe a different BP pattern between ischemic stroke subtypes, with cardioembolic stroke characterized by a lack of BP increase in the acute phase [47].

There is still some debate over the pathophysiological mechanisms underlying these changes and what they mean. Many contributing factors have been suggested and probably apply differently in different stroke types (ischemic or haemorrhagic) and subtypes (cortical or subcortical). The main ones include pre-existing high BP, activation of the neuroendocrine system (sympathetic, glucocorticoid, mineralocorticoid), increased cardiac output, the stress of hospitalization, and a Cushing reflex (reactive increases in systemic BP in response to raised intracranial pressure). Moreover, an extensive unilateral infarction in the region of the NTS may also induce neurogenic paroxysmal hypertension through a partial baroreflex dysfunction and increased sympathetic activity.

It is well known that CBF in acute stroke is dependent, largely, on systemic BP levels, which means that any changes in perfusion pressure can influence CBF and have important prognostic implications. Observational studies have shown a U-shaped relationship between BP immediately after stroke and clinical outcome. It has been suggested that a systolic BP around 150 mmHg could represent a positive prognostic factor [43], even though another study found the worst outcome to be associated with a rapid decrease in systolic BP and with baseline values both above and below 180 mmHg [7]. The risks of early recurrence and fatal cerebral oedema are each positively associated with admission systolic BP [78]. Infarct volume shows a U-shaped relationship with systolic and diastolic BP, but the target values for systolic BP are <160 and >200 mmHg. A lack of BP response during the acute phase of ischemic stroke is associated with a poor long-term outcome. Lacunar stroke and the highest BP on admission, carry the best prognosis, whereas the worst prognosis seems to be associated with cardioembolic stroke, involvement of the posterior circulation, and low BP [47, 70].

As of today only a few studies have examined the effect of BP reduction in acute ischemic stroke patients and data are still insufficient to make a recommendation on lowering or elevating BP in this setting of care [4]. The most recent international guidelines affirm that in most cases it is not imperative to lower BP in the acute phase and that hypertension should only be treated carefully and only when it is markedly elevated (Systolic BP ≥ 220 mmHg or diastolic BP ≥ 120 mmHg) with a goal of a 15% reduction in the first 24 hours after stroke. A previous antihypertensive regimen can be safely restarted within 24 hours of stroke onset in mild-to-moderate and neurological stable stroke [2].

Whereas an excessive increase in BP during the acute stroke phase could be a negative prognostic factor, the uncommon finding of low BP in this phase has also been suggested to be independently associated with a poor outcome. The ischemic penumbra, a region of the brain with a gradient of depressed CBF, is ischemic and dysfunctional but it can, potentially, survive for hours. With timely reperfusion this region may be saved from infarction; on the other hand, excessive BP reduction may lead to hypoperfusion of the penumbra and hasten extension of the infarct [79]. Anecdotal clinical reports of the use of induced hypertension to treat acute ischemic stroke date back to the 1950s. More recently, Chalela et al. [8] reported that phenylephrine infusion is able to improve cerebral perfusion without changes in cerebral blood volume. Hillis et al. [30] have performed a prospective, unblended study of induced hypertension in 15 consecutive ischemic stroke patients. They found that in treated patients the area of hypoperfusion showed a significant reduction in PWI lesion volume (from mean 132 to 58 ml, $P < 0.02$) and a significant reduction in the volume of diffusion-perfusion mismatch (from mean 83 l to 53 ml, $P < 0.005$). Although induced hypertension has never been widely adopted for ischemic stroke, it is now extensively used in neurocritical care units to treat delayed neurological deficits after subarachnoid haemorrhage. However the balance of benefit versus harm with induced hypertension in acute stroke need to be demonstrated in a large well-structured clinical trial and at the moment it cannot be recommended in clinical practice. Nevertheless possible hypotensive mechanisms are to be considered in the pathogenesis of stroke especially in patients with heart failure or autonomic insufficiency and therefore a consequent pressor therapy should be evaluated.

The acute cerebral ischemia can also deeply affect the cardiac autonomic control facilitating the occurrence of cardiac adverse events. The circadian rhythm of HR variability is found in a prospective study of Korpelainem et al. [37] to be reversibly abolished in the acute phase of ischemic stroke. At 6 months the circadian oscillation of HR returned. The loss of the relative vagal nocturnal dominance may contribute to the incidence of arrhythmias and other cardiovascular complication after ischemic stroke. In fact, in the first three months after acute ischemic stroke, 2–6% of patients die from cardiac causes. This cardiac risk is likely to be linked to the prevalence of ischemic heart disease and other comorbidities, but cerebral injury, inducing impaired function of the autonomic nervous system, including baroreflex function, may contribute directly to the generation of cardiac dysfunctions. Direct evidence, derived from autopsy studies, have confirmed that ECG abnormalities may occur even in the presence of normal coronary arteries and in the absence of acute ischemic changes, implying that they have a neurological rather than a primary cardiac cause [10, 11, 22, 71, 77]. At post-mortem examination, some patients with brain lesions have shown focal myocytolysis, myofibrillar degeneration, lipofuscin pigment deposition in myofibrils, and histiocytic infiltration of diffuse necrotic areas in the heart [28]. The focal myocytolysis involved intracardiac nerves rather than blood vessels, indicating possible neural origins. Its nature is still unclear, but plasma norepinephrine may be elevated after stroke and has been found to be associated with functional cardiac alteration in experimental models, indicating a sympathetic neural association [66]. Moreover, a high mean plasma norepinephrine concentration is associated with higher CK values, suggesting cardiac damage due to increased sympathetic activity.

Accurate prediction of cardiac complications early in the course of acute ischemic stroke could have a significant impact on the clinical management and on the outcome. High levels of cardiac troponin T (cTnT) or I (cTnI), which are considered the most accurate biomarkers of myocardial necrosis available in the clinical setting, are found in a substantial proportion of patients with stroke and are associated with poorer in-hospital prognosis. In particular, patients with abnormal, low (cTnI 0.1–0.39 ng/ml) and high (cTnI $\geq$ 0.4 ng/ml) cTnI levels on admission showed an increased risk of death of 2.1 and 2.5 respectively, and were also at increased risk of cardiac arrhythmias or ECG findings related to myocardial ischemia or necrosis [17]. However, at the present time there is no strong evidence that troponin elevations are due to neurologically mediated microvascular damage given that silent acute MI, heart failure and renal insufficiency are its most likely causes, and there is no threshold below which elevations of troponins are harmless and without negative prognostic implications [32].

A variety of arrhythmias have been shown to occur after stroke, with a reported incidence of new arrhythmias in admission ECGs ranging from 25 to 39% [26, 42]. Atrial fibrillation is the most common arrhythmia reported, occurring with a frequency of 9%. The overall incidence of new ventricular arrhythmias was found to be 8% in patients who were not continuously monitored. Using Holter data obtained from patients with transient ischemic attacks, cerebral infarction or intracerebral haemorrhage, the incidence of ventricular arrhythmias increased to between 24 and 60% [18].

Abnormal HR dynamics are independent predictors of all-cause mortality, and decreased HR variability is an independent predictor of one-year

mortality in patients with first-ever ischemic stroke. In addition, reduced baroreflex sensitivity in the acute phase of stroke is an independent predictor of all-cause mortality during a median four-year follow up.

In stroke patients, both cardiac arrhythmias and diffuse myocardial damage have been related to intense sympathetic nervous system activation, but abnormalities of the parasympathetic nervous system, too, may contribute to the autonomic imbalance in the acute phase of stroke.

Both right and left insular infarctions, due to their extensive autonomic and limbic connections, have been linked to cardiac derangement in humans. In particular two regions, one involving the right insula (posterior, superior and medial areas) and the other in the right inferior parietal lobule, have been found to be significantly associated with stroke-related myocardial injury. The insula, on account of its reciprocal connections with principal sensory areas, paralimbic areas in the orbital, temporopolar, and cingulated cortices, and the hypothalamus, is the site of integration of sensory, autonomic, and limbic functions. Insular stimulation studies in rats as well as in humans undergoing epilepsy surgery suggest that it is involved in cardiac autonomic control. Sympathetic responses in the heart can be elicited by stimulation of both the right and left, and anterior and posterior, insula, albeit to different degrees. There seems to be a right-sided dominance for sympathetic and a left-sided dominance for parasympathetic effects on the heart. It has also been suggested that there may exist an anteroposterior gradient responsible for more pronounced increases in HR and BP when the anteroventral insula is stimulated. In humans, right carotid amylobarbital infusion produces bradycardia, and left carotid infusion induces tachycardia [83]. Additionally, an increased incidence of supraventricular tachycardia was reported in patients with right MCA stroke [40]. In humans, left caudal anterior insular stimulation during surgery for intractable epilepsy increases the frequency of bradycardia and depressor responses, whereas stimulation of a similar region of the right anterior insula is associated with HR and diastolic BP elevation [56]. These data indicate that, in humans at least, some lateralisation of cardiovascular representation may exist, with predominantly sympathetic cardiovascular regulation being a right insula function, and parasympathetic cardiac neural regulation being related to the left insula.

In stroke patients, plasma norepinephrine and epinephrine concentrations have been found to be significantly higher in stroke involving the insular cortex than in non-insular infarctions; and this activation was more evident in right insular stroke. Stroke patients with right insular infarction were also characterized by higher systolic and diastolic BP values and HR. Moreover, stroke patients with lesions confined to the left insula, and consequently with higher basal heart rates, were more predisposed to developing ECG changes such as tachycardia, T wave inversion, prominent U waves and QTc prolongation. These abnormalities usually resolved within 2 months of stroke. In a recent study, Abboud et al. [1] found that acute brain infarction is independently associated with low HR (≤64 beats/minutes), abnormal repolarisation, atrial fibrillation, and ventricular and supraventricular ectopic beats. Brain infarctions involving the insula were characterized by significantly higher lesion volume, quantified using magnetic resonance imaging, and this difference was particularly marked for right-sided lesions ($P = 0.03$). Right insular stroke was significantly associated with two-year all-cause mortality (hazard ratio: 2.1, 95% CI: 1.27–3.52) and with vascular death (hazard ratio: 2.00, 95% CI: 1.00–3.93). In multivariate analysis, increased QTc interval and left bundle branch block (LBBB) were independent predictors of all-cause mortality and vascular death in right insular infarction patients. These data confirmed previous reports of increased mortality in right-sided insular infarction, supporting the hypothesis that acute strokes damaging the right insular cortex are associated with cardiac arrhythmias, which may contribute to vascular death. Increased QTc interval and the presence of LBBB in stroke survivors with right insular damage may serve as a useful, non-invasive marker for identifying patients at high risk of vascular death. However, Laowattana et al. [41] found that left insular, as opposed to right insular, stroke was associated with an increased risk of adverse cardiac outcome or cardiac wall motion impairment. In their study patients with left insular stroke without pre-existent coronary artery disease showed an increased rate of MI, angina pectoris and congestive heart failure or sudden death, with a relative risk of 1.75. A significantly worse outcome also detectable when concomitant cardiac disease was considered. These lateralisation differences may reflect the fact that the two insular areas regulate different components of the autonomic control of the heart. Additional studies of the effect of injury to each insular cortex will be necessary to determine the role of the right versus the left insular areas in human cardiac control.

At the end cardiovascular autonomic function may be impaired also in the post-acute stroke phase, but little data are available. In a recent study, Dütsch et al. [20] focused on the evaluation of the cardiovascular autonomic function 18 and 43 months after lacunar stroke. HF powers of RR_{int} were found to be reduced in patients after right and left-sided stroke ($P < 0.05$) and LF/HF ratio of RR_{int} was found to be elevated in

right-sided stroke patients as compared with left-sided stroke patients and controls. These data suggest a long-lasting parasympathetic cardiac deficit in stroke patients which could explain their increased risk of cardiac arrhythmia.

Conclusion

Although it is not often considered a pathogenetic factor in stroke or of stroke complications, ANS dysfunction should be evaluated in order to achieve a correct diagnostic and therapeutic approach to both of these pathological conditions. In fact, the ANS may contribute to the risk of atherothrombosis in stroke patients, promoting inflammation and coagulation, which can lead to the acute cerebrovascular events. These concepts suggest that a quite different approach to carotid pathology might be warranted. In particular, pharmacological modulation of autonomic balance, such as adrenergic blockade (which however may cause a decrease in cerebral perfusion pressure) [63], could be beneficial during acute phase of stroke, while interventional strategies such as carotid endarterectomy, angioplasty and stenting must be considered to worsen a pre-existing carotid sinus dysfunction through injury, material interposition, and balloon-induced baroreceptor trauma [23]. Heart rate and BP can fall sharply during carotid angioplasty or stent placement [46] inducing a dangerous acute hypotension which must be monitored and counteracted.

Most of the studies reported in this review cannot be considered conclusive. In some cases data concern different subtypes of stroke with different localization and the relationship between site and type of the lesion and cardiovascular manifestations may only be hypothesized. However, the ANS dysfunction may be responsible for the altered circadian rhythms subserving the onset of pathological processes that constitute risk factors of the stroke itself. On the other hand, stroke, through the alteration of areas and pathways regulating autonomic functions, may induce a variety of signs and symptoms otherwise difficult to explain.

Therefore this possible relationship between ANS function and dysfunction and stroke pathogenesis and occurrence represents a very intriguing area of investigation in neurology and vascular medicine.

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