Research Article

LACUNAR STROKE AND AUTONOMIC DYSFUNCTION

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Abstract

Objective: This study aimed to investigate the association between autonomic function and the lacunar strokes, along with a review of the literature to elucidate the interplay between the autonomic nervous system and stroke outcomes.

Methods: Thirty-two lacunar stroke patients and 28 healthy age matched control subjects were included. Sympathetic Skin Response (SSR) and R-R Interval Variation (RRIV) values were measured. In the both groups, SSR and R-RIV during rest and deep breathing were recorded for the assessment of sympathetic and parasympathetic function, respectively.

Results: The present study revealed significant differences in the autonomic function of patients with lacunar stroke compared with those in the control group. For the SSR, the patients showed a much lower amplitude and longer latency, indicating impaired sympathetic activity. Moreover, the R-R interval variability, both at rest and during deep breathing, was altered, suggesting changes in heart rate variability and parasympathetic function.

Conclusion: These study results highlight a marked autonomic dysfunction in patients with lacunar stroke, which has significant implications for clinical management and prognosis.
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Keywords: Lacunar Stroke; Autonomic Dysfunction; Sympathetic Skin Response; R-R Interval Variability; Sympathetic Function; Parasympathetic Function

Introduction

Stroke remains a leading cause of death and morbidity globally, and a significant proportion of survivors experience long-term sequel. The prevalence of post-stroke complications continues to pose substantial health challenges, particularly in developing nations [1]. The role of small vessel disease in stroke pathogenesis and its contribution to stroke outcomes necessitate further exploration, particularly with the increasing detection rates afforded by advanced imaging techniques [2].

Recent data suggest a wide-ranging prevalence of Autonomic Dysfunction (AD) in stroke patients, estimated at 10%-100%, reflecting the variability of presentation and diagnostic criteria [2-4]. Damage to the central autonomic networks, including but not limited to the insular cortex, has been implicated in the pathophysiology of AD in these patients [5]. However, the causal relationship between AD and stroke and its influence on prognosis remain unclear [6].

This study aimed to investigate the association between autonomic function and the laterality of lacunar strokes, along with a review of the literature to elucidate the interplay between the Autonomic Nervous System (ANS) and stroke outcomes, thus informing clinical management and shedding light on new studies for therapeutic interventions.

Materials and Methods

This study included consecutive patients diagnosed with lacunar stroke. Healthy individuals, paired with the patient group in terms of age and sex, were included in the study to form a control group. This study was approved by the institutional ethics review board and complied with the Declaration of Helsinki. Informed consent was obtained from

all patients participating in the study or from their legal representatives and individuals forming the control group. Exclusion criteria for patients and control group individuals were determined to be nervous system diseases and systemic diseases that may affect the ANS, drug use that may affect autonomic activity, and atrial fibrillation. This included conditions such as Parkinson's disease, multiple sclerosis, severe neuropathy, and significant cardiovascular diseases like myocardial infarction and heart failure, among others, which are known to independently impact autonomic function. The patient group comprised 14 women (43.8%), 18 men (56.3%), and 32 individuals. The control group comprised 28 healthy individuals: 14 females (50%) and 14 males (50%). The mean age of the patient group was 64.78 ± 13.09 (24-82) and the mean age of the control group was 64.28 ± 12.13 (30-84). All participants were questioned about the symptoms indicating Autonomic Nervous System (ANS) involvement, and systemic and neurological examinations were performed. Lacunar stroke was diagnosed by detecting infarcts smaller than 1.5 cm on Magnetic Resonance Imaging (MRI) of the brain in patients with neurological symptoms. The patient group was divided into right and left-sided infarcts, according to the direction of the lesion. The Body Mass Indices (BMI) of the patient and control groups was calculated in terms of their possible effect on R-R Interval Variability (R-RIV).

Sympathetic Skin Response (SSR) and R-R IV Analysis: Studies of SSR and R-RIV were performed within 30 days after the onset of stroke, at a temperature of 22°C-24°C, in a quiet room, while the patient was lying in a supine position. Both tests were applied to the patient and control groups between 10 am and 12 am. During the analysis, body temperature, arterial blood pressure, pulse, and blood electrolyte values were normal. A 4-channel electroneuromyography device (Nihon Kohden Neuropack 8, Model MEB 4200, and Tokyo, Japan) was used for recording. Sensitivity was set to 0.1-2 mV/div, analysis time was set to 0.5 sec/div, stimulation time was set to 0.2 m/sec, and filters were set to 0.5-3000 Hz in the electroneuromyography device for the study of SSR. The recordings were made with an Ag-AgCl electrode to avoid polarization. For recording, the electrodes were placed on the palm contralateral to the active lesion, the reference electrode was placed on the back of the hand, and the opposite side was recorded by giving an electrical warning to the median nerve at the wrist level of 15 mA or 20% more than the threshold that would create motor amplitude. In the control group, recordings were obtained using the right hand. The averages of the four SSRs were calculated by giving four stimulations at irregular intervals of 30-60 seconds. For the analysis of R-R IV, the filter was set to 20 Hz-50 Hz, sensitivity was set to 0.2 mV/div, analysis time was set to 0.2 sec/div in the electromyography device, and active and reference electrodes were placed on the back of the right and left hands. With these electrodes, temporal changes in the QRS waves relative to the triggering wave were recorded and superimposed. At rest, 32 waves were collected at a time, and this process was repeated five times (RR-RIV). The participants were then asked to perform deep breathing six times per minute, collecting 32 waves three times (DBR-RIV). The % ratio of R-R IV was calculated from measurements obtained from the collected waves at each time. The average of the measurements during rest and deep breathing were recorded. The obtained values were proportional to each other (R-RIVR) (R-RIVR=DBR-RIV/RR-RIV).

Statistical analysis

Data are expressed as n (%) and mean ± Standard Deviation (SD). The Kolmogorov-Smirnov test was performed to determine whether the data fit a normal distribution. The Student's t-test was used to compare the numerical data between the two groups. The chi-square test was used to compare categorical data, and the Pearson correlation test was used to investigate correlations between numerical data. The alpha error level was set at 0.05.

Results

In our analysis, autonomic function was assessed by measuring the SSR and R-R IV in patients with lacunar stroke compared with the control group. Lesions within the cerebral hemispheres were documented, with 15 cases (46.9%) demonstrating right hemisphere involvement and 17 cases (53.1%) showing left hemisphere involvement. The distribution of lesions was as follows: In the right hemisphere, 5 were in the basal ganglia and 10 in the centrum semiovale; in the left hemisphere, 8 were in the basal ganglia and 9 in the centrum semiovale.

No significant age or sex differences were noted between patients with right and left hemisphere

lesions (p=0.697 and p=0.265, respectively).

SSR amplitude and latency

The patient group exhibited a considerably lower SSR amplitude and longer latency than the control group. Lower SSR amplitude suggests a reduced sympathetic nervous system response, while longer latency indicates a delay in the initiation of this response. In clinical terms, this could imply a degree of sympathetic dysfunction or damage in the patient group, which is significant in the context of stroke since the autonomic nervous system plays a role in cardiovascular and other bodily functions that could be affected by stroke pathology (Table 1).

Table 1. Amplitude and latency of sympathetic skin response in patient and control groups.

SSR	Patient group (X ± sd)	Control group (X ± sd)	P
Amplitude (μV)	590 ± 395.85	1426.67 ± 614.05	<0.001
Latency (ms)	1675.99 ± 275.30	908.83 ± 213.63	<0.001

Note: *SSR: Sympathetic Skin Response; Amplitude: The peak value of the SSR wave, measured in microvolts (μV); Latency: The time interval between the onset of the stimulus and the occurrence of the SSR wave, measured in milliseconds (ms); **The data are presented as mean ± standard deviation (X ± sd); P=Paired t-test.

R-R interval variability

- The mean RR-RIV was higher in the patient group than in the control group. An increase in RR-RIV typically indicates greater variability in the time between heartbeats, which is often associated with increased parasympathetic activity. The parasympathetic nervous system slows the heart rate and increases Heart Rate Variability (HRV). Therefore, a higher mean RR-RIV in the patient group compared to the control group could suggest that the patients have a higher parasympathetic tone or activity.

- During DBR-RIV, a lower variability was noted in the patient group than in the control group. The lower variability in DBR-RIV in the patient group suggests a reduced autonomic flexibility compared to the control group. Typically, deep breathing is expected to induce greater HRV due to increased parasympathetic (vagal) activity.

- The R-RIVR, which is the ratio of R-R IV between deep breathing and rest, was significantly reduced in the patient group compared to the control group. The reduced ratio of R-R IV between deep breathing and rest (R-RIVR) in the patient group further indicates impaired autonomic responsiveness. The significant p-values in both measurements reinforce the reliability of these findings and imply that post-stroke patients may have compromised cardiac autonomic control (Table 2).

- The Body Mass Index was compared as a potential confounder, with no significant differences between the two groups (mean BMI for patients was 28.16 ± 5.29, and for controls, 26.96 ± 3.97; p=0.33). Additionally, BMI was not significantly correlated with SSR amplitude and latency or R-R IV measures in the patient group (p>0.05).

Table 2. R-R interval variability values in patient and control groups.

	Patient group (X ± sd)	Control group (X ± sd)	P
RR-RIV	17.08 ± 8.39	13.51 ± 3.94	0.044
DBR-RIV	19.41 ± 9.27	27.34 ± 7.06	0.001
R-RIVR	1,16 ± 0,26	2,07 ± 0,44	<0,001

Note: *R-RIV: R-R Interval Variability at rest; DBR-RIV: R-R Interval Variability during deep breathing; R-RIVR: Ratio of R-R Interval Variability between deep breathing and rest; **The data are presented as mean ± standard deviation (X ± sd); P= Paired t-test.

These findings suggest a substantial impairment of both sympathetic and parasympathetic functions in patients with lacunar stroke when compared to a healthy control group, independent of the lesion's hemispheric location and without the influence of BMI differences.

Discussion

Understanding stroke etiology is complex

and multifaceted yet essential for improving patient outcomes. This complexity is further compounded when considering the role of AD, which is observed in acute ischemic stroke and increasingly associated with prognosis [7]. AD, characterized by a disruption of the central autonomic network, manifests through alterations in the four hierarchical structures of the autonomic nervous system: the telencephalic, diencephalic, brain stem, and spinal levels [8,9].

The presence of AD in stroke patients, including those with extra insular lesions, underscores the extensive influence of the central autonomic network beyond the insula, which is traditionally considered a critical node for autonomic control [10-12]. However, the exact nature of the relationship between the autonomic system's integrity and stroke whether as a causative factor or a consequence remains elusive. This ambiguity persists despite the substantial evidence linking AD with the pathogenesis of atherosclerosis, a primary contributor to ischemic stroke [12,13].

In this context, our studies focused on lacunar infarcts, which despite their size, have significant implications for subcortical structures in the brain and are closely linked to autonomic irregularities. By examining the nuances of these small yet impactful cerebral events, we aimed to dissect the intricate interplay between focal cerebral ischemia and the cascading effects on the autonomic nervous system. The consequences of such dysfunction are not limited to immediate post-stroke outcomes but may also shape long-term recovery and quality of life for stroke survivors.

Lacunar infarcts and autonomic dysfunction: A reciprocal interplay

Lacunar strokes, stemming from occlusions in penetrating arteries, precipitate ischemic events that significantly disrupt the autonomic network of the brain. Despite their seemingly minor presentation, lacunar infarcts can lead to substantial ANS disruption, implicating crucial brain regions involved in autonomic regulation. Such disruptions are increasingly recognized for their enduring impact, potentially exacerbating long-term morbidity post-stroke, as posited in emerging research [14,15].

In our cohort, individuals with lacunar stroke exhibited notable impairments in SSR and parasympathetic activity, as evidenced by altered HRV metrics compared to healthy controls. This aligns with a growing body of evidence that underscores the pivotal role of autonomic regulation in the prognosis of stroke patients and may further advocate for the therapeutic targeting of autonomic pathways [12,16].

The findings of our study support the hypothesis that AD following lacunar stroke may play a critical role in patient outcomes, resonating with the wider discourse on neurovascular medicine. This underscores the need for integrative prognostic and predictive strategies that address the autonomic consequences of lacunar infarcts.

Autonomic function post-stroke: The significance of hemispheric roles and cerebrovascular reactivity

Exploring the realms beyond the traditionally emphasized insular cortex, our investigation revealed the broader implications of lacunar infarcts on autonomic function. This aligns with recent scholarly discourse suggesting a pivotal role of extra insular regions in autonomic regulation [4,12,17]. Our findings showed no significant correlation between stroke laterality and autonomic measures, echoing the notion of a non-lateralized, distributed autonomic network.

In the present study, we observed an increase in R-R IV at rest in patients with lacunar stroke, a counterintuitive finding considering the expected decrease due to parasympathetic influence. This paradox underscores the diminished parasympathetic activity post-stroke and reflects a shift from the traditional understanding of autonomic control centered on the insular cortex. The absence of insular involvement in our cohort suggests a more nuanced interplay within the central autonomic network, necessitating further research on the distributed nature of autonomic regulation post-stroke [3,18].

Our study corroborates the established association between acute AD and increased morbidity due to cardiovascular and infectious complications [19,20]. However, it also challenges the impact of lesion lateralization on autonomic outcomes, proposing a more complex interaction than previously acknowledged. The unique profile of lacunar stroke, characterized by reduced SSR amplitude and prolonged latency, calls for a re-evaluation of the stroke-ANS relationship, highlighting the significance of lacunar infarcts in shaping AD and its prognostic implications.

AD is a recognized sequel of both major and minor stroke. Studies have delineated the distinct roles of the cerebral hemispheres, with the right hemisphere predominating in sympathetic modulation and the left hemisphere predominating in parasympathetic functions, particularly when considering the brain-heart axis [15,21]. Notably, instances of concurrent sympathetic and parasympathetic dysfunction emanating from a singular hemisphere have been documented, highlighting the complex interplay within autonomic networks [22,23].

Crucially, cerebrovascular reactivity, an index of the brain's vascular responsiveness, has emerged as a key player in the context of ischemic strokes, including lacunar strokes. A reduction in cerebrovascular reactivity may suggest a reduction in parasympathetic activity, which has been corroborated by the present study's findings. These observations necessitate further exploration of whether such autonomic alterations are a direct consequence of lacunar infarcts or secondary to hypertensive responses [22].

While AD has been associated with factors such as male sex, stroke severity, and insular cortex involvement, correlating with poorer prognoses, it appears to be largely independent of age, hemispheric lateralization, and the presence of comorbidities [24]. Autonomic disturbances are seen in the acute phase of ischemic stroke and can persist, with a preponderance of parasympathetic over sympathetic dysfunction [2].

The implications of these autonomic irregularities are profound, contributing to the risk stratification of patients with stroke and potentially guiding early intervention strategies. The burgeoning evidence underscores the importance of a nuanced understanding of autonomic sequel post-stroke and their implications on patient recovery and long-term outcomes [3,16].

A comprehensive understanding of the role of cerebral hemodynamics and their correlation with parasympathetic activity reduction in lacunar infarcts is crucial. This insight is not merely academic but also has tangible implications for early stroke management strategies and long-term patient care. Future research should continue to disentangle the intricate mechanisms at play, particularly by examining the broader impact of AD across various stroke subtypes and its potential as a target for therapeutic intervention.

The complexities of the autonomic nervous system with its extensive cerebral and peripheral connections remain a vast field of research. Recognizing the full scope of the contribution of AD to stroke prognosis and the necessity for targeted therapeutic approaches will be instrumental in advancing stroke recovery and rehabilitation practices.

Body mass index as a confounding factor

Our analysis further indicated that BMI does not significantly confound the relationship between lacunar stroke and AD. This lends weight to the argument that the observed autonomic changes are primarily a consequence of stroke pathology rather than the secondary effects of other systemic factors.

To further elucidate the relationship between BMI and AD after lacunar stroke, our data aligned with findings from cardiovascular studies on type 2 diabetes and hypertension [25]. Ko et al., suggested that cardiovascular autonomic neuropathy can predict acute ischemic stroke in diabetic patients, indicating a possible prognostic role for AD [26]. Similarly, a study by Halima et al., discussed the similarity in AD between acute coronary syndrome and ischemic atherothrombotic stroke patients irrespective of BMI [27]. These studies reinforce the notion that autonomic changes post-stroke are likely intrinsic to cerebrovascular events rather than merely secondary to systemic conditions such as obesity or diabetes. This perspective prompts a deeper examination of stroke pathology and its primary effects on autonomic integrity, which is potentially independent of other cardiovascular risk factors.

Study limitations and considerations for future research

In recognizing the limitations of our current study and anticipating future research directions, we must consider several factors. Although adequate for preliminary insights, the sample size of our study may not capture the full spectrum of AD after a lacunar stroke. Larger cohorts are needed to confirm these findings and ensure that they are representative of a wider population. Additionally, the specificity of our focus on lacunar strokes calls for expansion in subsequent studies to include other stroke subtypes that may exhibit different patterns of autonomic disruption.

The duration of our follow-up period also necessitated an extension. While our study

provides a snapshot of the acute phase up to six months post-stroke, the long-term trajectory of autonomic recovery or decline remains unclear. Ongoing monitoring beyond the acute and sub-acute phases of stroke can provide invaluable data on chronic autonomic changes and their impact on patient outcomes.

Furthermore, given the complexities of stroke pathophysiology and its systemic effects, interdisciplinary research incorporating cardio logical, neurological and rehabilitative perspectives could yield a more comprehensive understanding. This approach may also foster the development of novel therapeutic strategies aimed at modulating the autonomic nervous system to improve recovery and reduce the risk of recurrent strokes. Such strategies may include personalized rehabilitation programs with a focus on parasympathetic activation, targeted pharmacotherapy to enhance autonomic balance, and non-invasive neuromodulator techniques like transcutaneous vagal nerve stimulation, tailored to individual patient profiles to optimize recovery outcomes.

Conclusion

Considering the findings from our study and the corroborating literature, we conclude that lacunar strokes significantly influence autonomic function, independent of insular cortex involvement. Despite their small size, lacunar infarcts have substantial impacts on the autonomic nervous system, affecting both sympathetic and parasympathetic activities and potentially altering long-term stroke outcomes. The lack of BMI's influence on autonomic changes suggests that these are inherent to stroke pathology. Future research should expand on these insights with larger, more diverse cohorts to fully understand the mechanisms and therapeutic implications of AD in stroke recovery.

Declarations

Ethical approval

This thesis was approved by the Faculty Council of Cumhuriyet University Faculty of Medicine on 12.03.2002 date and decision No. 2002/1 and the Rector of Cumhuriyet University on 28.03.2002 according to the 'Thesis Writing Guide,' which is considered appropriate with the date and article No. 463. Thesis no: 243278.

This thesis has been transformed into an article in light of the current information.

Consent for publication

Detailed consent was obtained from all participants during the preparation of this thesis.

Competing interests

The author has no conflicts of interest to declare.

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Authors' contributions

S. E. analyzed and interpreted the patient data regarding the collecting data, applied statistical tests, and analyzed the data.

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