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AUTONOMIC FUNCTIONS IN PATIENTS WITH STROKE: A COMPARISON WITH LOCATION OF VASCULAR INSULT

İNMELİ HASTALARDA OTONOMİK FONKSİYONLAR: VASKÜLER TUTULUMUN YERİ İLE KARŞILAŞTIRMA

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ABSTRACT

Objective: We aimed to investigate sympathetic and parasympathetic nervous system functions in patients with stroke and to correlate with localization of vascular insults.

Materials and methods: Sympathetic skin response (SSR) of both upper extremity and RR interval variation (RRIV) during rest and deep breathing were recorded in 56 patients with stroke and 42 healthy volunteers.

Results: The mean latency of SSR of either side in patients with stroke (both in affected side and unaffected side) significantly prolonged as compared to those in controls ($p<0.05$). Mean amplitudes of the responses of either extremity in patients with stroke (0.8±0.6 mV in affected side, 0.9±0.8 mV in unaffected side) were significantly smaller than in controls (1.4±0.9 mV) ($p<0.001$, $p<0.01$). RRIV during rest in patients compared to controls were 30.97± 27.99 versus 16.5±5.1 and during deep breathing were 34.2±25.2 versus 19.9±8.6 ($p<0.05$). Based on the localization of infarcts, lesions were classified as hemispheric (n=46) and brain stem (n=10). Patients with hemispheric lesions had significantly increased latencies ($p<0.05$) and depressed amplitudes ($p<0.001$), increased RRIV at rest ($p<0.001$) and during hyperventilation ($p<0.001$) as compared to controls. RRIV during rest and during deep breath were both higher in the right-sided cortical lesions than left sided cortical lesions ($p<0.05$, $p<0.01$). Increased SSR latencies from affected hands and decreased amplitudes from non-affected hands of brain stem lesions recorded than controls' ($p<0.05$).

Conclusion: As a result, vascular insults of cerebrum, mainly right-sided cortical structures affect sympathetic and parasympathetic functions. Brain stem vascular lesions were characterized by involvement of sympathetic reflex activity.

Key words: Stroke, sympathetic skin response, autonomic system

ÖZET

Amaç: Çalışmamızın amacı; inmeli hastaların sempatik ve parasempatik sistem fonksiyonlarını araştırmak ve vasküler tutulumun yeri ile ilişkisini incelemekti.

Gereç ve yöntem: Her iki üst ekstremitenin sempatik deri yanıtı (SSR) ve RR interval varyasyonları (RRIV) inmeli 56 hasta ve 42 sağlıklı gönüllüde istirahat ve derin nefes sırasında kayıt edildi.

Bulgular: İnmeli hastaların her iki (etkilenen ve etkilenmeyen) tarafının ortalama SSR latansları kontrollerinki ile karşılaştırıldığında anlamlı olarak uzamıştı ($p<0,05$). İnmeli hastaların her iki ekstremitesinden elde edilen ortalama amplitüdler (0,8±0,6 mV etkilenen, 0,9±0,8 mV etkilenmeyen) kontrollerden anlamlı olarak daha küçüktü (1,4 ±0,9 mV) ($p<0,001$, $p<0,01$). Hastalarda istirahatte RRIV'ler kontrollerle karşılaştırıldığında 30,97± 27,99 karşı 16,5±5,1 ve derin nefes alma ile 34,2±25,2 karşı 19,9±8,6 idi ($p<0,05$). İnfarkt lokalizasyonuna göre lezyonlar hemisferik (n=46) ve beyin sapı olarak sınıflandı (n=10). Hemisferik lezyonlu hastaların kontroller ile karşılaştırıldığında anlamlı olarak artmış latansları vardı ($p<0,05$) ve amplitüdleri düşüktü ($p<0,001$), istirahat ($p<0,001$) ve hiperventilasyon sırasında ($p<0,001$) RRIV artmıştı. İstirahat ve derin nefes ile RRIV'nin her ikisi sağ taraf kortikal lezyonlarında sol taraf kortikal lezyonlarından daha yüksekti ($p<0,05$, $p<0,01$). Beyin sapı lezyonlarının etkilenen ellerinden artmış SSR latansları ve etkilenmeyen ellerinden azalmış amplitüdleri kontrollere göre kayıt edilmiştir ($p<0,05$).

Sonuç: Sonuç olarak beyin damar tutulumlarında esas olarak sağ taraf kortikal lezyonları sempatik ve parasempatik fonksiyonları etkilendi. Beyin sapı vasküler lezyonları sadece sempatik refleks aktivitenin tutulumu ile karakterize idi.

Anahtar kelimeler: İnme, sempatik deri yanıtları, otonom sistem

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INTRODUCTION

Several organ systems are affected secondary to central nervous system dysfunctions caused by vascular insults in different locations. Involvement of the autonomic nervous system appears with various organ system symptoms and findings. Some symptoms are related to the localization of vascular insult (9,23,26). Experimental studies have demonstrated autonomic dysfunctions secondary to hemispheric involvement (8,15,20). Studies on autonomic functions in patients with stroke have conflicting results. Oppenheimer et al.(19) reported several cardiac disturbances as arrhythmia or ischemic disease in patients with stroke and these changes were secondary to hyperactivity of sympathetic system. However, several studies demonstrated suppression of sympathetic reflex response and decreased parasympathetic cardiac innervations (3,13,15). Furthermore, some stroke-related autonomic abnormalities appear more relevant in patients with right-sided hemispheric infarctions (4,6) and right insular cortex is believed to play a major role in the autonomic modulation of cardiac activity (5,17). Left insular stroke found with an increased risk of poor cardiac outcome and decreased cardiac wall motion compared to stroke in other locations and TIA, in a study (14). Exact mechanism and the localization of the effective cortical areas are not known. Sympathetic skin response (SSR) and R-R interval variation (RRIV) are simple, quick, easily applicable and noninvasive tests for clinical evaluation of the autonomic functions. These tests evaluate reflex sympathetic activity and parasympathetic vagal function (1,16,24).

We aimed to record SSR and RRIV in patients with chronic stroke for evaluation autonomic functions and compared them with the localization of lesions.

MATERIAL and METHODS

Patient group consists of 56 (35 male) patients with stroke aged 32 to 76 (61.09±11.15) years and 42 (26 male) healthy volunteers aged 35 to 73 (58.71±8.63) years. There were not statistically significant difference for age and sex ratio between healthy and stroke groups. Duration of stroke in patients ranged 2 to 38 (6.69±7.29) months. None of them were in acute phase. 46 stroke patients were ischemic stroke, 10 patients were hemorrhagic stroke.

Patients with previously diagnosed reflex sympathetic dystrophy, peripheral neuropathy, carpal tunnel syndrome, lesions of brachial plexus, systemic diseases, which may involve peripheral and autonomic nervous system such as diabetes mellitus or uremia or patients on medications, which affects sympathetic or parasympathetic nervous system were excluded.

Computed tomography (n=31) or magnetic resonance imaging (n=25) revealed hemispheral lesions in 46 patients [cortical (n=27) and subcortical (n=19)] and brainstem lesions in 10 patients. Hemiplegia or hemiparesis of right side was present in 27 patients. 22 patients in cortical lesions' had insular cortex involvements.

The patients were informed about the aim and method of the study and informed consent was obtained from themselves or caregivers of the patients with global aphasia.

Recording Techniques: The electrophysiological tests were performed in a semi-darkened and silent room. During the testing, all patients were lying in supine position. Room temperature was maintained at 23°C and bilateral palmar temperatures were verified to be greater than 32°C. And if they were below 32°C, the limbs were heated up by covering with a blanket.

ESAOTE electroneuromyography device was used. For SSR recordings, 6 mm disc electrodes were used. To stimulate median nerve at the wrist, active electrode was placed on the palm, reference electrode on the dorsum of the hand, and ground electrode on the forearm. The distance between the stimulator and recording electrodes was 8 cm. SSR in patients with stroke was recorded on the involved hand after stimulation of the ipsilateral median nerve and on the healthy hand after stimulation of the ipsilateral median nerve. To avoid any habituation, stimulations were made with randomized intervals and various intensities. A sensitivity of 500μV-2mV per division and sweep speed of 1-2 sec was used for recording. Low -and high -frequency filters were adjusted as 0.1 and 1000 Hz. The duration of the stimulus was between 0.1 and 0.2 msec and the stimulus intensity ranged 10 mA to 40 mA. If we did not elicit any response to 10 consecutive stimuli, the response was accepted to be absent. The latency was measured from the onset of the stimulus artifact to the first deflection of the signal baseline and the amplitude was measured from peak to peak.

RRIV was recorded using the same electrodes placed to the dorsum of each hand after a period of 30 min supine rest and deep breathing (6 times per min). Thirty-two recordings were done during rest and forced deep breathing. A sensitivity of 500μV per division and sweep speed of 2 sec was used for recording. Low -and high -frequency filters were adjusted as 20 and 100 Hz.

In the determination of RRIV we used the formula RRIV=a/bx100, Where the difference between the earliest and latest R waves was identified as "a" and the mean of RR intervals was termed as "b". RRIV recorded at rest was termed as R% and the one that recorded hyperventilation was symbolized as DB% (24).

The recording parameters used for SSR and RRIV are demonstrated in Statistical analyses were done by statistical package for social sciences. X^2 test was used for evaluation of gender in groups. Means of age, SSR or RRIV in two groups compared to each other by independent sample t test and comparison of means of SSR or RRIV for localizations of lesions were performed by one-way ANOVA (Analysis of Variance), Post Hoc Multiple Comparison and Kruskal Wallis tests.

RESULTS

SSR were elicited at all upper extremities from all subjects, except three patients with hemiplegia who did not have any responses in the affected side. RRIV during rest and deep breathing was not recorded in one patient with pacemaker, because no comparable change was noted. Six patients with global aphasia did not deeply breathe due to lack of cooperation. RRIV were obtained in the remaining of patients and all controls.

Mean latencies of SSR in both sides were significantly longer than in controls ($p<0.05$). Mean amplitudes of responses in affected or unaffected side were depressed compared to that in controls ($p<0.001$, $p<0.01$) (Table 1).

Mean RRIV during rest and deep breathing significantly were increased compared to controls ($p<0.05$) (Table 2).

Table 1. Comparison of sympathetic skin response latency and amplitude values in the patients and controls.

	n	Latency (sec)* mean±SD	Amplitude(mV)** mean±SD
Control	42	1.27±0.14	1.42± 0. 89
Patients	56		
Affected side	53	1.38±0.29 *	0.83±0.62 ‡
Unaffected side	56	1.41±0.34 * *	0.91±0.77 †

Independent stuent t test with control * p<0.05, **p<0.05, † p<0.01, ‡ p<0.001 ANOVA *F=3.176 **F=4.7 (p<0.05)

Table 2. Comparison of R-R Interval Variation percentages in the patients and controls.

	n	**R%** (mean±SD)	n	**DB%** (mean±SD)
Control	42	16.53±5.09	42	19.88 ± 8.6
Patients	55	30.97 ± 27.99*	49	34.19 ± 25.18**

R% : rest RRIV; DB%: deep breathing RRIV Independent stuent t test *p <0.05 **p <0.05

Patients with lesions involving one of cerebral hemispheres had significantly prolonged latencies of SSRs in affected and unaffected side (p<0.05), depressed amplitudes of responses (p<0.001 for affected hand and p<0.01 for unaffected hand) and increased RRIV at rest or during deep ventilation (p<0.01) compared to controls (Tables 3 and 4).

Mean latency of SSR in affected hand in patients with brain stem involvement was significantly longer and mean amplitude of unaffected side was significantly smaller than in controls (p<0.05). The remaining parameters of SSR or RRIV were not significantly changed compared to controls (Table 3 and 4).

Table 3. Comparison of sympathetic skin response latency and amplitude values according to localization of lesions.

	n	**Latency(sec)** (mean±SD)	**Amplitüde(mV)** (mean±SD)
Control	42	1.27±0.14	1.42± 0. 89
Hemispheral lesion	46		
Affected side	44	1.38±0.29 *	0.77±0.6 ‡
Unaffected side	46	1.41±0.35 *	0.92±0.76 †
Brain stem lesion	10		
Affected side	9	1.45±0.34 *	1.04±0.69
Unaffected side	10	1.44±0.31	0.83±0.8 *

* p<0.05, † p<0.01, ‡ p<0.001

Table 4. Comparison of R-R Interval Variation percentages according to localization of lesions.

	n	**R%**(mean±SD)*	n	**DB%**(mean±SD)**
Control	42	16.53±5.03	42	19.88±8.5
Hemispheral lesio	45	32.5±29.0*	39	35.05±26.02*
Brain stem lesion	10	22.37±21.02	10	29.08±21.32

*p<0.01

No differences of SSR and RRIV variables in both limbs were found between patients with hemispheric lesion and the patients with brainstem lesions. But RRIV variables were found statistically significant differences between the patients with right-sided cortical lesions and the patients with left sided cortical lesions (for RRIV during deep ventilation, p<0.01; for RRIV at rest, p<0.05) (Table 5). RRIV variables were found statistically significant different in right insular cortex involvement than left insular cortex involvement among cortex lesions during deep ventilation and at rest (p<0.05).

Table 5. Comparison of R-R Interval Variation percentages according to side of cortical lesions.

	N	**R%**(mean±SD)	**N**	**DB%**(mean±SD)
Left sided	13	30.9±29.0	12	23.47± 8.94
Right sided	14	41.83±36.83*	10	41.43± 30.89†

* p<0.05, † p<0.01

DISCUSSION

Our data revealed that sympathetic and parasympathetic nervous system is affected in patients with subacute or chronic stroke. Sympathetic dysfunction characterized by prolonged latency and depressed amplitude of SSR was demonstrated not only by stimulation of hemiplegic extremity, but also by contralateral side. A few studies reported similar results (7,13) in some studies, although, the most prominent abnormality in patients with chronic stroke was depressed amplitude of SSR and minimally or unaffected latency of the response (1,18). Korpelainen (13) reported that suppression of mean amplitudes was a constant finding during acute phase of stroke, whereas prolonged latencies normalized during chronic phase. Zimmerman et al (26) demonstrated that chronic stroke caused a significantly prolonged latency only on the left hemiplegic side.

Pathways of SSR is not definetly known (7,13,15). Mesencephalic reticular formation, thalamus, hypothalamus and brain stem are important structures of sympathetic system (2,5,15). In brain stem lesions, the disturbances of the SSR are likely to be caused by destruction of the sympathetic sudomotor pathway, which descends from the hypothalamus via mesencephalon, pons, and posterolateral medulla oblongata to the intermediolateral column of spinal cord (13). It has been also considered that cerebral cortex has an important role in modification of sympathetic response (13,22). The presence of bilateral abnormalities of SSR in all our patients, even in patients with brain stem lesions is in favor of a central dysregulation of the response rather than involvement of afferent or efferent pathways.

Similar to our data, Korpelainen et al. (13) studied SSR in patients with different localizations of infarcts and found the maximum dysfunction in patients with hemispheric involvement and the minimum dysfunction in patients with brain stem involvement. Our SSR measurements were correlated those findings too. Uncini et al.(25) demonstrated that extension of a lesion rather than its location (cortical versus subcortical) was indicative of the reproducibility of SSR.

We found significantly increased RRIV during rest and deep breathing in patients with stroke. Contrary to our data, previous studies usually reported decreased RRIV in patients

with stroke (3,7,12). Increased RRIV during rest and deep breathing were interpreted as an indication of parasympathetic dysfunction or decreased cardiac parasympathetic innervation. In the normally innervated heart, sympathetic-parasympathetic interactions regulate myocardial excitability and cardiac rhythm. Sympathetic stimulation increases sinoatrial depolarization. Vagal stimulation, on the other hand, slows depolarization of the sinus node and increases electrical stability. In central disorders, a strong relationship between sympathetic involvement and cardiac arrhythmias was demonstrated (21). The role of parasympathetic activity, in contrast, is not so clear. We think that depression of sympathetic activity is compensated by a relative increase in cardiovagal activity.

The insular cortex has been implicated in the control of cardiac autonomic function in humans and animals (4-6,14,17) RRIV of right-sided cortical lesions were increased according to left cortical lesions and both of them were higher than controls' RRIV. And RRIVs of both cortical sides' were higher than RRIVs of subcortical's and controls'. Studies were reported that right-sided hemispheric lesions were found more related with autonomic dysfunctions (4-6,17). Our results were consistent with their findings. Several experimental and clinic studies determined insular involvement in stroke and all of them which reported right insular involvement found an important role on autonomic dysfunctions and cardiac variability (4,6,17). We found statistically significance in RRIV of groups according to insular involvement of both sides even if groups had limited patient number. And our findings may suggest a major role of right insula in the pathogenesis of cerebrogenic cardiac disturbances. But there was data on left insular stroke with adverse cardiac outcome too (14).

Studies about heart rate variability measures demonstrated reduced parasympathetic function after stroke (12). Korpelainen et al (10) reported that their results from the patients' heart rate variability with hemispheric stroke were not different significantly from those with medullary brainstem stroke at 6 months after stroke, our findings were similar to those of Korpelainen but one of the limitations of our study is relatively low numbers of subjects. It may affect our results.

In the present study, autonomic dysfunction was most evident in patients with hemispheric lesions. Mean latencies and amplitudes of SSR of all upper extremities and RRIV in patients with hemispheric lesions were affected whereas only latencies of SSR in affected side and amplitudes in unaffected side were involved in patients with brainstem lesions. Korpelainen et al recorded low SSR amplitudes on the ipsilateral and contralateral sides to the lesions in stroke patients. Which were consisted with our results (13). The brain stem stroke patients with vasomotor reflex asymmetry all had symptoms suggesting disorder of spinothalamic pathways. Authors has been reported that after brain stem strokes, ipsilateral hemihypohydrosis resulting from damage to uncrossed hypothalamic spinal pathways regulating sweating was occurred in their sudomotor dysfunction studies (11). In our study ipsilateral brain stem finding may be explain with uncrossed hypothalamo- reticulo- spinal pathway.

In addition, our findings support the opinion that parasympathetic activity is represented predominantly in the right hemisphere, right cortical (with and without insular involvement), and right insular cortex lesions play a significant role in autonomic regulation.

In conclusion, sympathetic and parasympathetic dysfunction occurs in patients with subacute or chronic stroke, affecting mainly cerebral hemispheres. We suggest longitudinal follow-up studies with larger patient groups to check the reliability of SSR and RRIV as a screening test of autonomic dysfunction in patients with stroke.

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