

Autonomic Nervous System Modifications During Wakefulness and Sleep in a Cohort of Patients with Acute Ischemic Stroke

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Goal: The aims of our study were to investigate autonomic modifications in wakefulness and sleep in a cohort of patients with acute ischemic stroke and to evaluate whereas these modifications were dependent by sleep stage and stroke lateralization. *Materials and Methods:* We prospectively enrolled 42 patients (22 men and 20 women, mean age: 69.8 ± 11.3 ; range: 32-92 years) with acute ischemic stroke. All participants underwent a full-night polysomnography. As index of autonomic nervous system we used Heart Rate Variability (HRV), analyzed in wakefulness and during different sleep stages. First, we compared our cohort with a control group of 42 healthy subjects, matched for age and sex. Subsequently, we divided our cohort in 2 subgroups according stroke lateralization (21 right, 21 left) and compared with control population. *Findings:* We observed significant modifications of HRV parameters mainly for the right lesions. In particular, we observed a prevalent parasympathetic tone during the wake (low frequency/high frequency [LF/HF]: right: 2.99 ± 8.91 ; controls: 3.88 ± 3.42 ; $P < .01$) and during REM (LF/HF right: 0.03 ± 1.58 ; controls: 2.92 ± 3.97 ; $P < .01$) accompanied by a significant reduction of sympathetic tone during REM (LF right: 23.85 ± 44.42 n.u.; controls: 51.13 ± 32.25 n.u.; $P < .01$), and by a reduction of parasympathetic tone during N3 (HF right: 28.09 ± 37.67 n.u.; controls: 43.08 ± 68.39 n.u.; $P < .01$). *Conclusions:* Our study indicates that autonomic dysfunctions in acute ischemic stroke are prevalent in right-side lesions and strictly dependent by sleep-wake stage.

Key Words: Autonomic nervous system—Stroke—Sleep—Heart rate variability—Dysautonomia—Acute stroke
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Background

Autonomic nervous system (ANS) dysfunctions are commonly observed in acute stroke,¹ particularly in the right hemisphere stroke^{2,3} and in the lesions of the insula.^{4,5} Stroke dysautonomia could result in an altered autonomic cardiac control: about 4% of patients with

acute ischemic stroke die within the first 3 months from cardiac causes and 19% experience adverse cardiac events, with higher risk 2-3 days poststroke.⁶

The activity of ANS recognizes several modifications in the physiological sleep-wake cycle, following circadian (sleep versus wake) and ultradian (Non-REM versus REM) pattern. During wakefulness, the sympatho-vagal balance changes continuously in order to maintain body homeostasis. During Non-REM (NREM) sleep, the parasympathetic tone increases resulting in a reduction of heart rate and blood pressure from lighter to deeper sleep.⁷ During REM sleep, autonomic activity shows great variability characterized by burst of sympathetic tone similar to those observed during wakefulness.⁸

Clinical deterioration after acute ischemic stroke is prevalent during night-time.⁹ In acute stroke, sleep is disrupted and fragmented.¹⁰ ANS dysfunction during sleep in acute stroke has been poorly studied. It is possible to hypothesize that autonomic dysfunction is exaggerated

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during the sleep compared to the wakefulness, with a disruption of circadian (wake-sleep cycle) and ultradian (NREM-REM cycle) rhythms.

On these bases, the aims of our study were to evaluate autonomic modifications in acute ischemic stroke and whereas these modifications were dependent on stroke lateralization and on sleep-wake stages.

Methods

Patients

We prospectively enrolled 42 patients (22 men and 20 women, mean age: 69.8 ± 11.3 ; range: 32-92 years) with acute ischemic stroke recruited from the Stroke Unit of Fondazione Policlinico Universitario A. Gemelli. Inclusion criteria were the diagnosis of ischemic stroke, confirmed by neuroimaging, NIHSS (National Institute of Health Stroke Scale) greater than 0, and informed consent to participate in the study. The exclusion criteria were the inability of the patient to undergo to the polysomnography (PSG) and the lack of consent to participate. The study was performed in accordance with the declaration of Helsinki.

For each patient, the following data were recorded: age, gender, stroke lateralization, NIHSS, atrial fibrillation, obstructive sleep apnea (OSA), troponin elevation, hypertension, diabetes, hypercholesterolemia, internal carotid stenosis $\geq 50\%$, thrombophilia, heart disease, prior cerebrovascular event, smoke, patent foramen ovale, OCSF (Oxfordshire Community Stroke Project) classification, TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification, ASPECTS (Alberta Stroke Program Early CT Score) score, chronic therapies in use at the moment of the index event. Clinical characteristics of patients are reported in Table 1.

Controls

Patients were compared with a control group of 42 healthy subjects, matched for age and sex: 22 men and 20 women (mean age: 66.0 ± 6.8 ; range: 54-81 years). The same exclusion criteria were applied to patients as well as to the control group.

Polysomnography

Patients underwent a full-night, unattended, nocturnal PSG within 3 days of stroke onset. PSG were recorded by a Micromed System (Micromed, Mogliano Veneto, Treviso, Italy) Morpheus digital polygraph. Montages included 3 electroencephalogram (EEG) leads applied to the following locations: Fp1, C3, O1; reference electrodes applied to the right (A2) mastoid; 2 electrooculographic electrodes applied to the cantus of each eye, surface electromyography of submental and intercostal muscles, air-flow measured by oro-nasal thermocouple, thoracic and abdominal effort, snoring detector, electrocardiogram (EKG), and peripheral hemoglobin saturation. Impedances were kept below $5 \text{ K}\Omega$ before starting the recording,

and checked again at the end of the recording. Sampling frequency was 256 Hz, A/D conversion was made at 16 bit. Preamplifier amplitude range was $\pm 3.200 \mu\text{V}$, and prefilters were set at 0.15 Hz. Sleep monitoring lasted from 17:00 to 07:00 the next morning.

Heart Rate Variability

As index of ANS we used Heart Rate Variability (HRV). HRV study was carried on the EKG trace obtained in the PSG study. According to established criteria, the EKG was recorded by using a modified lead II derivation (with the right shoulder negative and the left lower torso positive). Sampling rate was 256 Hz, with a digital resolution of 16 bits per sample. Impedance was kept below $5 \text{ K}\Omega$.

HRV analysis was performed in frequency-domain and in time-domain exclusively for mean heart rate. In the frequency-domain, HRV was analyzed by means of the parametric Autoregressive Model analysis which allows an accurate estimation of Power Spectral Density when analyzing short time intervals during which the signal is supposed to maintain stationary.^{11,12} The frequency bands considered were the low frequency (LF, 0.04-0.15 Hz) and the high frequency (HF, 0.15-0.4 Hz) ones. The power of LF and HF bands was expressed in normalized units (n.u.), and the LF/HF ratio was calculated. A detailed description of HRV analysis, standards of measurement, physiological interpretation, and clinical use is available in the report of the task-force of the European Society of Cardiology and the North American Society of pacing and electrophysiology.^{11,12}

All patients and controls were evaluated at the following times: first consecutive 5 minutes of quite wake (W), light sleep (N2), slow wave sleep (N3), and REM sleep (REM).

Physiological mechanisms of heart period modulations responsible for LF and HF power components cannot be considered stationary during the long-lasting periods of sleep.^{11,12} Therefore, the decision to evaluate sleep intervals of 5 minutes was motivated by the necessity to collect homogenous samples of EKG from homogeneous samples of each sleep stage, of comparable duration, without interruptions due to EEG arousals, stage shifts, or awakenings. Artifact rejection was performed visually. A dedicated software (Rembrandt SleepView, Medcare) recognized the individual electrocardiographic R wave peaks and calculated the R-R intervals (tachogram). Successively, the tachogram, an Excel file, was converted into an ASCII file and analyzed by means of a dedicated freeware (HRV Analysis Software, Biomedical Signal analysis Group, Dept. of Applied Physics, University of Kuopio, Finland).¹³

Statistical Analysis

Before comparing the 2 groups (stroke versus control), the normality of distribution of age of the samples has been tested by means of the Shapiro-Wilk test, with a significance level of $P < .05$; the distribution was not normal

Table 1. Risk factors

	Sex	Age	OSA	HT	DM	AF	IHD	Cholesterol >200 mg/dl	Trombophilia	Carotid disease > 50%	Smoke	PFO	Stroke/TIA
# 1	F	77	1	1	1	1	0	0	0	0	1		0
# 2	F	56	0	1	1	0	0	0	0	0	0		0
# 3	F	84	1	1	0	1	0	0	0	0	0		1
# 4	F	82	0	1	0	0	0	0	0	0	0		1
# 5	F	71	1	1	0	1	0	1	0	0	0		0
# 6	F	70	0	0	0	0	0	0	0	0	0	1	0
# 7	F	77	1	1	0	1	0	1	0	0	0		0
# 8	F	81	0	1	0	0	0	0	0	0	0		0
# 9	F	65	1	1	0	0	0	1	0	1	1		0
# 10	M	52	1	0	0	0	0	0	0	0	1	1	1
# 11	F	78	1	1	0	1	0	0	0	0	0		0
# 12	M	68	1	0	0	0	0	0	1	0	0		0
# 13	M	65	1	1	1	0	1	1	0	0	0		0
# 14	M	71	1	1	0	1	1	1	0	0	1		0
# 15	F	64	0	1	0	1	0	0	0	0	0	0	1
# 16	M	74	1	1	1	0	0	0	0	0	0		0
# 17	M	70	1	1	1	0	1	1	0	0	0		1
# 18	F	67	1	1	1	1	0	0	0	0	0		0
# 19	M	67	1	1	0	0	0	1	0	1	0		0
# 20	F	56	0	0	0	0	0	1	0	1	0		0
# 21	M	57	1	1	1	0	0	0	0	0	0		1
# 22	F	86	0	1	1	1	1	1	0	1	0		0
# 23	M	62	1	0	0	0	0	0	0	1	1		0
# 24	M	67	0	1	0	0	0	0	0	0	0	1	1
# 25	M	67	1	1	0	1	0	0	1	0	0		0
# 26	F	92		1	0	0	1	0	0	0	0		0
# 27	M	32	1	1	1	0	0	1	1	0	1	0	0
# 28	F	62	0	0	0	0	0	0	0	1	0		0
# 29	M	71	1	0	1	0	0	0	0	0	0		0
# 30	M	75	1	1	1	0	0	0	0	0	0		0
# 31	F	70	1	1	0	0	0	0	0	0	0		0
# 32	M	66	1	1	0	0	1	0	0	1	0		0
# 33	F	84	1	1	1	1	1	0	0	1	0		0
# 34	M	84	1	1	0	1	0	0	0	1	0		0
# 35	M	69	0	1	1	0	1	1	0	0	1		0
# 36	M	64	1	1	0	0	0	0	0	0	0		0
# 37	F	81	1	1	0	1	0	0	0	0	1	0	0

(Continued)

Table 1 (Continued)

Sex	Age	OSA	HT	DM	AF	IHD	Cholesterol >200 mg/dl	Trombophilia	Carotid disease > 50%	Smoke	PFO	Stroke/TIA
#38	55	1	0	1	0	0	0	0	0	0	0	0
#39	73	0	1	0	0	0	1	0	0	1	0	0
#40	77	0	1	1	0	0	0	0	0	0	0	1
#41	85	0	1	0	0	0	0	0	1	1	0	0
#42	56	1	0	0	0	0	1	0	0	0	1	0
Mean	69.8											
SD	11.3											
N	22	28	33	15	13	8	13	3	10	10	4	8
%	M: 52.4 F: 47.6	66.7	78.6	35.7	31.0	19.0	31.0	7.1	23.8	23.8	9.5	19.0

Abbreviation: OSA, Obstructive Sleep Apnea; HT, Hypertension; DM, Diabetes Mellitus; AF, Atrial Fibrillation; IHD, Ischemic Heart Disease; PFO, Patent Forame Ovale; TIA: Transient Ischemic Attack.

and therefore we compared HRV parameters using a non-parametric test (Mann-Whitney *U*-test). Subsequently we compared HRV parameters in 3 subgroups: controls, right and left stroke; a nonparametric test was applied (Kruskal-Wallis 1-way analysis of variance). Significance level was set at $P < .05$.

In case of multiple comparisons, in order to avoid family-wise type-I errors, a formal Bonferroni correction was applied to each family of comparisons, by dividing the limit of significance by the number of comparisons (for numeric parameters 4 comparisons were made, in the following conditions: W, N2, N3, and REM sleep stages; therefore the significance level was set at $P = .05/4 = .0125$).

Finally we compared right stroke versus left stroke for associated conditions: numeric variables were compared by means of 1-way analysis of variance Mann-Whitney *U*-test; nominal variables were analyzed and compared by Pearson's χ^2 test.

Statistics were performed by means of the Statistical Package for Social Science (SPSS) software version 20.

Results

We prospectively enrolled 42 patients with acute ischemic stroke: 22 men (52.4%) and 20 women (47.6%) (mean age: 69.76 ± 11.32 ; range: 32-92 years).

Associated conditions have been evaluated in all our patients; particularly, OSA and hypertension were prominent in our population. Detailed prevalence of associated conditions of the study population is reported in Table 1.

Ischemic stroke was located in the right hemisphere in 21 patients and in left hemisphere in 21 patients; mean NIHSS at admission was 9.31 ± 7.08 ; mean ASPECTS was 5.97 ± 2.61 . Clinical syndromes were classified according OSCP classification and stroke etiology according the TOAST classification. Stroke lateralization, NIHSS, ASPECTS, OSCP, TOAST, and acute therapeutic intervention are reported in Table 2.

In the comparison between stroke patients and controls for HRV, significant differences were observed in: mean heart rate during the wake (stroke: 73.80 ± 13.42 ; controls: 61.39 ± 9.31 ; Mann-Whitney $U = 1345.00$; $P < .01$) and during N2 (stroke: 67.11 ± 11.63 ; controls: 55.25 ± 10.55 ; Mann-Whitney $U = 1191.00$; $P < .01$), LF/HF during wake (stroke: 2.42 ± 6.50 ; controls: 3.88 ± 3.42 ; Mann-Whitney $U = 463.00$; $P < .01$), and HF during N3 (stroke: 39.71 ± 74.82 ; controls: 56.46 ± 30.69 ; Mann-Whitney $U = 408.00$; $P < .01$). For details see Table 3.

Subsequently we compared right stroke, left stroke, and controls. There were no significant differences in the comparison between right and left stroke for associated conditions, NIHSS, ASPECTS, and for clinical syndromes. Significant differences were observed in mean heart rate during the wake (right: 74.60 ± 12.72 ; left: 72.97 ± 14.41 ; controls: 61.39 ± 9.31 ; $P < .01$) and mean heart rate during

Table 2. Stroke lateralization, classification and acute treatment

	Lateralization	TOAST	OCSF	ASPECT score	NIHSS admission	Thrombolysis	Thrombectomy
# 1	R	CE	PACS	4	19	1	0
# 2	R	SUE	LACS	8	3	0	0
# 3	L	CE	TACS	3	19	0	0
# 4	L	SUE	POCS		4	0	0
# 5	R	CE	PACS	5	15	0	0
# 6	R	PCE	PACS	9	3	0	0
# 7	R	CE	PACS	5	14	0	0
# 8	L	SUE	PACS	7	10	1	0
# 9	L	LAA	PACS	7	7	0	0
# 10	L	PCE	PACS	6	3	0	0
# 11	L	CE	PACS	7	14	1	0
# 12	R	SODE	PACS	9	2	0	0
# 13	R	SUE	POCS		5	0	0
# 14	L	CE	PACS	6	14	1	0
# 15	R	CE	PACS	4	15	0	0
# 16	R	SVO	LACS	9	2	0	0
# 17	R	CE	PACS	6	13	1	0
# 18	L	CE	PACS	7	6	0	0
# 19	L	LAA	PACS	7	4	0	0
# 20	L	LAA	PACS	7	17	1	0
# 21	R	SUE	LACS	8	11	1	0
# 22	L	SUE	TACS	7	23	0	1
# 23	L	LAA	PACS	8	2	0	0
# 24	R	PCE	POCS		2	0	0
# 25	R	SUE	POCS		8	0	0
# 26	L	PCE	PACS	9	10	0	0
# 27	R	CE	TACS	1	16	1	1
# 28	R	LAA	TACS	0	21	0	0
# 29	L	SVO	LACS	9	2	0	0
# 30	L	SUE	TACS	2	21	1	1
# 31	R	PCE	PACS	6	3	0	0
# 32	L	LAA	PACS	9	3	0	0
# 33	R	CE	TACS	3	21	0	0
# 34	R	CE	POCS		4	0	0
# 35	R	CE	POCS	1	3	0	0
# 36	L	LAA	POCS		14	1	0
# 37	L	CE	TACS	4	22	1	0
# 38	L	SUE	POCS		4	0	0
# 39	R	PCE	POCS		2	0	0
# 40	R	SUE	POCS		2	0	0
# 41	L	LAA	PACS	8	7	0	0
# 42	L	PCE	PACS		1	0	0
Mean				5.97	9.31		
SD				2.61	7.08		
%	R: 50%, L: 50%	CE: 33.3% PCE: 16.7% SUE: 23.8% LAA: 19.0% SVO: 4.8% SODE: 2.4%	TACS: 16.7% PACS: 50.0% LACS: 9.5% POCS: 23.8%			26.19%	7.14%

Abbreviation: R, Right; L, Left; TACS, Total Anterior Circulation Syndrome; PACS, Partial Anterior Circulation Syndrome; LACS, Lacunar Syndrome; POCS, Posterior Circulation Syndrome; CE, Cardioembolism; PCE, Possible Cardioembolic; LAA, Large-Artery Occlusion; SVO, Small Vessel Occlusion; SODE, Stroke of Other Determined Etiology; SUE, Stroke of Undetermined Etiology.

Table 3. Comparison of HRV parameters between stroke group and controls

Sex	Controls		Stroke		
	22M, 20F		22M, 20F		
	Mean	SD	Mean	SD	
Age (yrs)	66.05	6.83	69.76	11.32	
Mean HR (bpm) W	61.39	9.31	73.80	13.42	Mann-Whitney $U = 1345.00$; $P < .01$
HF W	33.92	22.27	39.81	44.82	
LF W	41.21	25.95	23.15	41.40	
LF/HF ratio W	3.88	3.42	2.42	6.50	Mann-Whitney $U = 463.00$; $P < .01$
Mean HR (bpm) N2	55.25	10.55	67.11	11.63	Mann-Whitney $U = 1191.00$; $P < .01$
HF N2	32.73	19.52	40.17	37.49	
LF N2	37.04	23.80	30.69	51.79	
LF/HF ratio N2	2.13	3.35	1.17	2.15	
Mean HR (bpm) N3	59.87	16.56	67.05	12.08	
HF N3	56.46	30.69	39.71	74.82	Mann-Whitney $U = 408.00$; $P < .01$
LF N3	27.85	22.68	31.49	66.90	
LF/HF ratio N3	0.66	0.80	0.91	1.56	
Mean HR (bpm) REM	67.44	10.42	66.69	10.37	
HF REM	43.08	68.39	30.43	28.75	
LF REM	51.13	32.25	34.57	37.16	
LF/HF ratio REM	2.92	3.97	1.25	2.34	

Abbreviations: HR, Heart Rate; HF, High-Frequency; LF, Low-Frequency; W, Wakefulness; N2, N2 Sleep; N3, N3 Sleep; REM, REM sleep; bpm, Beats Per Minute.

the N2 (right: 68.90 ± 10.36 ; left: 65.33 ± 10.36 ; controls: 55.25 ± 10.55 ; $P < .01$). The analysis of frequency domain parameters showed significant differences for LF/HF during wake (right: 2.99 ± 8.91 ; left: 1.82 ± 2.31 ; controls: 3.88 ± 3.42 ; $P < .01$) and during REM (right: 0.03 ± 1.58 ; left: 2.31 ± 2.41 ; controls: 2.92 ± 3.97 ; $P < .01$); significant differences were also observed for LF during REM (right: 23.85 ± 44.42 ; left: 43.95 ± 27.53 ; controls: 51.13 ± 32.25 ; $P < .01$) and HF during N3 (right 28.09 ± 37.67 ; left: 55.56 ± 68.93 ; controls: 43.08 ± 68.39 ; $P < .01$). Therefore, we performed post-hoc analysis. Significant increase of mean heart was evident during wake in both right (right: 74.60 ± 12.72 ; controls: 61.39 ± 9.31 ; $P < .01$) and left stroke (left: 72.97 ± 14.41 ; controls: 61.39 ± 9.31 ; $P < .01$) when compared with controls. Increased mean heart rate was still significant during the N2 for both right (right: 68.90 ± 10.36 ; controls: 55.25 ± 10.55 ; $P < .01$) and left stroke (left: 65.33 ± 10.36 ; controls: 55.25 ± 10.55 ; $P < .01$). The analysis of frequency domain parameters showed significant differences for: LF/HF during wake for right versus controls (right: 2.99 ± 8.91 ; controls: 3.88 ± 3.42 ; $P < .01$), during REM for right versus controls (right: 0.03 ± 1.58 ; controls: 2.92 ± 3.97 ; $P < .01$) and for right versus left (right: 0.03 ± 1.58 ; left: 2.31 ± 2.41 ; $P < .01$). Finally, significant differences were observed for LF during REM for right versus controls (right: 23.85 ± 44.42 ; controls: 51.13 ± 32.25 ; $P < .01$) and HF during N3 for right versus controls (28.09 ± 37.67 ; controls: 43.08 ± 68.39 ; $P < .01$). Detailed results are reported in [Table 4](#).

No significant differences were observed for the prevalence of associated conditions between right and left strokes.

Discussion

Our results indicate that acute ischemic stroke is associated with dysregulation of the activity of the ANS. These modifications are prevalent in right lesions and are dependent by sleep-wake stage.

First, we observed increased mean heart rate in both right and left stroke compared with controls; this increase was significant during wakefulness and light sleep. The mean heart rate was still higher during deep sleep, whereas, during REM sleep no difference has been observed in mean heart rate in stroke patients compared with control. Increased heart rate is widely reported in stroke patients during wake and sleep¹⁴ but no data are available for the sleep stages.

The analysis of HRV parameters in the frequency domain showed a reduction of LF/HF ratio in stroke group during the wakefulness and REM sleep. These results permit to hypothesize a prevalence of parasympathetic tone, during wakefulness and REM sleep, in acute stroke. In the subgroups analysis according stroke lateralization, these differences were confirmed only for right lesions. According to the idea that right hemisphere is involved in the control of sympathetic nervous system (SNS),² it is possible to assert that in ischemic lesion of right hemisphere a sympathetic dysfunction is prevalent.

Table 4. Comparison of HRV parameters between left stroke, right stroke and controls

	Left stroke		Right stroke		Controls		
	Mean	SD	Mean	SD	Mean	SD	
Mean HR (bpm) W	72.97	14.41	74.60	12.72	61.39	9.31	L versus C $P < .01$; R versus C $P < .01$
HF W	27.62	11.92	51.42	59.93	33.92	22.27	
LF W	33.63	27.20	13.17	50.10	41.21	25.95	
LF/HF ratio W	1.82	2.13	2.99	8.91	3.88	3.42	R versus C $P < .01$;
Mean HR (bpm) N2	65.33	12.82	68.90	10.36	55.25	10.55	L versus C $P < .01$; R versus C $P < .01$
HF N2	27.59	32.77	38.56	37.88	32.73	19.52	
LF N2	48.51	56.53	31.20	53.13	37.04	23.80	
LF/HF ratio N2	1.41	2.16	1.22	2.20	2.13	3.35	
Mean HR (bpm) N3	63.76	12.27	70.77	11.09	59.87	16.56	
HF N3	55.56	68.93	21.75	79.46	56.46	30.69	R versus C $P < .01$
LF N3	28.14	19.22	35.28	97.26	27.85	22.68	
LF/HF ratio N3	0.84	0.70	0.98	2.20	0.66	0.80	
Mean HR (bpm) REM	64.57	8.99	69.11	11.60	67.44	10.42	
HF REM	32.49	18.96	28.09	37.67	43.08	68.39	
LF REM	43.95	27.53	23.85	44.42	51.13	32.25	R versus C $P < .01$
LF/HF ratio REM	2.31	2.41	0.03	1.58	2.92	3.97	R versus C $P < 0.01$; R versus L $P < .01$

Abbreviations: HR, heart rate; HF, high-frequency; LF, low-frequency; W, wakefulness; N2, N2 sleep; N3, N3 sleep; REM, REM sleep; bpm, beats per minute.

This hypothesis is also supported by the reduction of LF in patients with right hemispheric stroke during REM. Interpretation of LF component of HRV is controversial: some studies suggest that LF is a quantitative marker of SNS instead other studies indicate that reflects both vagal and sympathetic activity.¹⁵ This component reflects, at least in part, the activity of SNS; therefore, we considered this finding as a correlate of decreased sympathetic activity in REM sleep in right stroke.

Conversely, the role of vagal activity as major contributor to the HF component has been demonstrated in clinical and experimental observations.¹² We found significant reduction of HF in the stroke group during N3 sleep, indicating a marked reduction of vagal tone. In the subgroup analysis this reduction was prominent for right stroke. This observation confirms the results of the only study that evaluate HRV during acute phase of stroke in the sleep.¹⁶ It is possible to suppose that the parasympathetic suppression observed during deep sleep in our patients could result in altered cardiac control or in modification of cerebral blood flow and, in turn, in a poor outcome.

Regarding stroke lateralization, our data are in line with previous literature. A reduction of parasympathetic HRV components in right stroke compared with left stroke has first been described by Naver et al,¹⁷ conversely, other studies suggest an increased sympathetic tone.¹⁸ Increased autonomic dysfunction in both right ischemic and hemorrhagic strokes is reported in literature,¹⁹ suggesting a prominent role of right hemisphere, and in particular of the right insula, in the control of sympatho-vagal balance. Our findings support that right hemisphere is crucial for the modulation of the activity of ANS.

ANS dysfunction during sleep in the acute stroke has been poorly studied. Korpelainen et al²⁰ evaluated HRV during night and day hours and in acute and chronic phase in patients with hemispheric brain or brainstem infarction; the author observed an abolished circadian oscillation of ANS activity in acute stroke patients regardless of the lateralization or clinical severity of stroke. Interestingly, circadian oscillation returned normal at 6 months, suggesting that ANS dysfunction is reversible. The observed differences between the patients and the control subjects were most pronounced during the night, suggesting a state dependent (wake/sleep) alteration of ANS in acute ischemic stroke.

Giubilei et al studied HRV during sleep in 10 patients with acute ischemic stroke. During stroke acute phase, the researchers found a decreased parasympathetic activity and a sympathetic predominance in wakefulness and in sleep; the sympathetic predominance was still present at the 3-week follow-up. However, HRV components, in this study, showed a significant change in the comparison between wake and sleep, suggesting a physiological circadian pattern. On these basis, they suggested that despite the altered autonomic control due to cerebral ischemia and characterized by increased sympathetic tone, the physiological changes in sympathetic and parasympathetic activity during sleep are preserved.¹⁶

In healthy subjects the sympatho-vagal balance is strictly dependent by sleep-wake stage and changes deeply in sleep-wake transition and during the different sleep stages. In fact, there is a prevalence sympathetic activity during the wake and a progressive shift toward parasympathetic activity with increasing sleep depth with the maximum of the vagal tone during N3 sleep stage.

Conversely, an increased shift to sympathetic modulation, comparable with that observed during wakefulness, is characteristic of REM sleep. In our cohort of ischemic stroke patients, and in particular in those who had right hemispheric lesions, we observed exactly the opposite cycle of the ANS in the acute phase of the stroke: a relative predominance of vagal tone during wakefulness and REM sleep and a relative predominance of sympathetic tone during slow wave sleep. This data suggest that in acute phase of stroke, and in particular in right hemispheric stroke, the physiological balance of ANS is completely altered resulting in a disruption of circadian and ultradian rhythm of the activity of ANS. Therefore, we hypothesized that the ability of ANS to modulate this activity is compromised in acute stroke.

A more complete understanding of brain and dysfunction of ANS during sleep could open new therapeutic strategies involving sleep modulation.

ANS dysfunction is a frequent complication of stroke, particularly in the right lesions, and it can be detrimental for the clinical outcome. Therefore, this could be a new therapeutic target for the pharmacological modulation of autonomic balance.

Conclusions

Our study indicates that ANS dysfunction is present in acute ischemic stroke, particularly in right-side lesions. The modifications of the activity of ANS are strictly dependent by sleep-wake stage. The adaptability is one of the peculiar characteristics of ANS; our data suggest that in acute stroke a flexible and dynamic system becomes stiff, unable to adapt to the physiological homeostasis. ANS modulation can be an intriguing therapeutic target in acute stroke.

Limitations

We compared our study population with a control group of healthy subjects; therefore, we could not adjust the effect of associated conditions (such as diabetes, OSA, and atrial fibrillation) on ANS activity in our study population.

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