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Research Article

Cardiac Autonomic Dysfunction After Cortical Ischemic Stroke: Does Side Really Matter?

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Abstract

Background: Sudden cardiac death due to arrhythmia and associated E.C.G abnormalities are common among stroke survivors. Stroke is known to damage the central autonomic pathway which in turn causes significant cardiovascular dysfunction and arrhythmogenesis. Heart Rate Variability (H.R.V) is a commonly used measure for studying cardiovascular autonomic modulation. Therefore we felt studying H.R.V could throw some light on cardiovascular autonomic balance post stroke. Thus H.R.V and cardiovascular reflex autonomic function tests were compared between right hemispheric and left hemispheric stroke patients.

Materials and Methods: It was a cross sectional study involving 25 patients (left = 13, right = 12) after various duration post ischemic stroke ranging from 3 to 6 months. The ischemic stroke was verified by C.T scan and or M.R.I scan immediately post stroke. Inclusion criteria were: age group 45-75, first stroke, absence of significant carotid stenosis, absence of intracranial haemorrhage. Patients with major concurrent medical illness and those on drugs affecting the A.N.S were excluded. E.C.G was recorded for 5 minutes after 10 minutes of rest with the patients lying in supine position according to task force guidelines. Time domain, Frequency domain and Non linear analysis of H.R.V was conducted. Standard battery of autonomic function tests were carried out on all patients.

Results: Among the frequency domain parameters VLF, LF and Total power were significantly reduced on left sided stroke patients. Though there was no significant difference in time domain parameters between right and left hemispheric ischemic stroke, rMSSD was reduced and SDNN was higher after right sided stroke. However there was no effect of lateralization of stroke on the standard battery of cardiac autonomic function tests.

Conclusion: There is a relatively higher sympathetic tone after right stroke as denoted by a higher LF and Total Power and a higher LF/HF ratio. Clinical autonomic tests did not show any significant difference between left and right groups.

Keywords: Autonomic Nervous System; Ischemic Stroke; Heart Rate Variability; Sudden Cardiac Death; Arrhythmia

Introduction

Majority of strokes are ischemic [27]. Stroke has been known to cause serious cardiac arrhythmias and cardiovascular changes the most dangerous consequence of this is a tendency towards sudden cardiac death [8]. These arrhythmias may result from damage to neural pathways that are known to control the autonomic nervous system (A.N.S) [11]. In the cortical region, insular cortex (within the middle cerebral artery territory) is known to be the most important in controlling both the sympathetic and parasympathetic function [3]. Other cerebral centres include cingulate gyrus, amygdala and orbito frontal area [2].

The most common clinical problems after a stroke include abnormalities in heart rate and blood pressure regulation reflecting cardiovascular autonomic dysfunction, and asymmetric sweating

with cold hemiplegic limbs, reflecting changes in the sudomotor and vasomotor regulatory systems. Bladder and bowel dysfunction and impotence are also frequent complaints after stroke, but the present knowledge concerning their prevalence and clinical significance is still limited. Cardiovascular autonomic dysfunction, which is mainly related to increased sympathetic activity, is most evident in the acute phase of stroke, whereas other autonomic disorders, such as abnormal sweating, are long-standing or even irreversible. In addition to the well-established sympathetic hyper function, abnormalities of the parasympathetic nervous system may also contribute to the autonomic imbalance after stroke.

Heart rate variability (H.R.V) is a physiological phenomenon which reflects the change in the influence of the A.N.S on the work done on the heart [15]. In a Framingham heart study on elderly subjects low H.R.V was related to increased risk of cardiac arrhythmias and to sudden cardiac death after myocardial infarction [10]. H.R.V is superior to left ventricular ejection fraction in predicting arrhythmic events such as ventricular tachycardia. Low H.R.V is particularly related to sudden cardiac death [25]. Power spectral analysis of H.R.V may further help in separation of patients into low risk and high risk of sudden cardiac death [19]. Hemispheric brain infarction seems to result in a significant dysfunction of autonomic cardio regulatory system manifesting as a reduced H.R.V [14].

Materials and Methods

This study was conducted in the Department of Physiology of V.M.M.C and Safdarjung Hospital, New Delhi from October 2012 to March 2014 in collaboration with the department of Neurology, Safdarjung Hospital and department of Radio diagnosis, Safdarjung Hospital. The ethics committee of the medical faculty, Safdarjung Hospital approved the study and each subject provided written informed consent. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The patients with a recent history of stroke were recruited from the neurology outpatient department where they came for follow up. All of the patients had to fulfil the following criteria: First episode of stroke within the last one year, no neurological impairment before the stroke, evidence of ischemic lesion in neuroimaging study (CT or MRI) consistent with the clinical manifestations, sinus rhythm in ECG.

Exclusion criteria were 1) History of any major form of concurrent cardiac disease 2) intracranial haemorrhage or symptoms of raised intracranial pressure 3) any major concurrent illness including renal failure, pulmonary disease and malignancies. 4) Peripheral diabetic neuropathy which impairs autonomic function 5) fever 6) alterations in consciousness or any relevant hemodynamic compromise.

Cerebral CT and/or MRI had been done during the admission and the reports were already available. In MRI Stroke volumes were quantified by outlining abnormalities on T2-weighted FLAIR images. Patients with stroke volume bigger than two third of the middle cerebral artery (M.C.A) territory were excluded. Stroke severity assessed using the National Institute of Health Stroke Severity Scale (NIHSS) was available from the case records. Carotid Doppler ultrasonography and echocardiography reports from the time of admission were also available.

Once the patients were recruited in the Outpatient department they were called for the electrophysiological tests at a later date. The electrophysiological tests were carried out in a semi darkened and silent room. The room temperature was maintained at 23^0C. Blood pressure was continuously monitored by non invasive blood pressure amplifier (NIBP 100D by Biopac). This instrument uses a double finger cuff to generate a continuous arterial blood pressure waveform similar to a pulse wave form.

All the patients underwent short term (5min.) E.C.G recordings using Biopac MP 150 system and Acqnowledge (version 4.2) software. The sampling rate was 256 Hz. HRV analysis was done with the help of Kubios HRV pro version software (University of Kuopio, Kuopio, Finland).

The digital E.C.G signals were analysed online and stored on a hard disk for offline use. Time domain measures were derived after re-sampling and interpolating the R-R intervals. Frequency domain HRV analysis was performed by Fast Fourier transform based Welch periodogram. Standard frequency domains were used as defined by the Task Force. Non linear parameters of HRV were also assessed.

Protocol of clinical autonomic tests

The standard battery of tests was used for assessment of parasympathetic and sympathetic reactivity [9].

Parasympathetic tests

- Deep Breathing Test: A baseline recording of E.C.G was done for 30 seconds. The patient was visually guided to breathe slowly and deeply at 6 cycles per minute. The E: I ratio was calculated from the largest R-R interval during expiration and smallest R-R interval during inspiration. The average ratio of six cycles was calculated for each subject. A ratio of 1.21 was considered normal.
- Valsalva manoeuvre: A baseline E.C.G was recorded. The subject was instructed to blow into a mouth piece attached to a sphygmomanometer to raise the pressure to 40mmhg for 15 sec. Valsalva ratio was calculated from the maximal R-R interval during phase IV and smallest R-R interval during phase II. Ratio greater than 1.21 was considered normal.
- Lying to standing tests: supine blood pressure was measured and the subject was stand upright in 3 sec. Maximum fall in systolic B.P within 3 minutes of orthostasis was noted.
- Head up tilt test: Subject was asked to lie down in the supine position on a head up tilt table 5 minutes prior to tilt. Supine blood pressure was measured. Table was tilted within 15 sec. for 70^0 (approximately 5 degrees / sec). The table was kept in that position for 5 minutes. Maximum fall in B.P during 3 minutes of orthostasis was noted. 30:15 ratios were calculated for maximum R-R interval at around 30 sec and minimum R-R interval at around 15 secs.

During tilt test a fall more than 10mm Hg systolic blood pressure and 30:15 ratio more than 1.04 was considered normal.

Sympathetic tests

- Cold pressor test: Baseline blood pressure was measured. The subjects hand was immersed into cold water (10^0C for 1 min) and rise in diastolic blood pressure at the end of 1 min was noted. A rise in diastolic blood pressure of 10mmHg was considered normal.
- Handgrip test: The baseline blood pressure was measured. Subject was asked to hold hand grip dynamometer at 30% of their maximum voluntary contraction (MVC) for 4 min. The rise in diastolic blood pressure during tilt was measured. Rise of more than 10mmHg in DBP was considered normal.

Ewing's classification of autonomic failure

Results for each autonomic test were classified as normal, borderline and abnormal. Ewing's classification of autonomic failure was determined as shown below for each participant [6].

1. Normal – all tests are normal or borderline
2. Early- one of the heart rate tests abnormal or 2 borderline
3. Definite – 2 or more heart rate tests abnormal
4. Severe – 2 or more heart rate tests abnormal or both borderline plus 1 or both B.P test abnormal or both borderline.
5. Atypical – any other combination

Statistical analysis

All analysis was carried out using IBM SPSS 21 software. We separated subjects with MCA infarct into 2 groups based on lesion hemisphere. Descriptive statistics were generated for all variables. Categorical variables were represented as numbers (percentages). Continuous variables were presented as mean +/- s.e.m. To compare mean age between right and left stroke Mann Whitney U test was used. For other nominal group characteristics like diabetic status, hypertension and smoking Chi Square test was used. Distribution of mNIHSS score again being a nominal variable was compared using Fischer's exact test. Continuous variables like heart rate, SDNN, NN50, SD1, sample entropy, total power, LF/HF ratio were found to be non parametric and hence Mann- Whitney U test was used. The other continuous variables VLF, LF, HF, meanHR, RMSSD, PNN50, SD2, Shannon entropy were found to be parametric and hence independent samples t-test was used for the comparison. Group differences in severity of autonomic dysfunction were tested using Fischer's exact test. In each of the above comparisons p value <0.05 was considered significant.

Results

- Group characteristics: When comparing the distribution of demographic variables between the right and left stroke we observed no difference between the 2 groups for sex distribution, hypertension status, and alcoholism [ref. table 1]. Therefore we rightly assume that these factors did not affect the outcome. When comparing the stroke lateralization with the stroke severity we find that there is no difference in overall stroke severity between the 2 groups as assessed by modified NIHSS scoring [ref. table 2]. Hence the 2 groups were comparable in terms of severity.
- Effect of infarct hemisphere on frequency domain measures: Power spectral analysis showed that VLF, LF and TOTAL POWER were significantly higher on the right side. This could reflect a relatively higher sympathetic tone after right MCA stroke compared to the left [ref. table 3]. LF/HF ratio which denotes sympathovagal balance was higher after right sided stroke although it was not significantly different.
- Effect of infarct hemisphere on time domain measures: Though we found a significant difference in mean heart rate which was reduced on right hemispheric stroke the time domain analysis did not show any difference between the 2 groups [ref. table 4]. NN50 was significantly higher after right stroke. The time domain analysis has a limited use in short term recordings of E.C.G.
- Effect of infarct hemisphere on non linear HRV measures: Among non linear measures of H.R.V, SD2 and Shannon entropy showed a significantly higher value among left sided stroke patients [ref table 5]. Earlier studies have not demonstrated the effect of lateralization on non-linear H.R.V indices

- Effect of infarct hemisphere on stage of autonomic failure: The patients were classified into 5 stages of Ewing's autonomic failure and the distribution of these 5 stages among right and left hemispheric stroke was compared. Analysis showed no difference in distribution between the 2 groups [ref table 6]. To our knowledge this is the first study to classify the stroke patients into different stages of autonomic failure so as to study the effect of lateralization.

Demographic Parameters	Stroke		P value
	LH stroke (n=13)	RH stroke (n=12)	
Age	55.923 ± 8.68	57.92 ± 18.44	0.320††
Diabetics	n (%)	n (%)	
Yes	7(53.85)	4(91.67)	0.428†
No	6(46.15)	8(8.33)	
Hypertension			
Yes	8 (61.53)	5(41.67)	0.434+
No	5(38.47)	7(51.33)	
History of Smoking			
Yes	7(53.85)	5(41.67)	0.695+
No	6 (46.15)	7 (51.33)	
History of alcoholism			
Yes	4(30.76)	1 (8.33)	0.322†
No	9(69.24)	11(91.67)	

Table 1: Distribution of Group characteristics.
RH stroke – right MCA stroke, LH stroke – left MCA stroke.
Percentages are column-wise
† P value obtained through Fisher's exact test
†† p value obtained through Mann- Whitney U test
+ p value obtained through Pearson chi- square test

mNIHSS score group	Infarction location		p value†
	RH stroke (n=12)	LH stroke (n=13)	
	n (%)	n (%)	0.322
1-4	7 (58.33)	5 (33.33)	
5-15	4 (33.33)	8 (67.33)	
16-20	1 (8.33)	0	

Table 2: Comparison between Stroke Lateralization and Stroke Severity

RH stroke – right MCA stroke, LH stroke – left MCA stroke.

% - column percentage.

† p value obtained through Fisher's exact test.

Frequency domain parameter	RH stroke (12) Mean +/_ S.E.M(n)	LH stroke (13) Mean +/_ S.E.M(n)	P value
VLF(ms^2)	419.9+/_64.99(7)	153.6+/_43.16(7)	**0.005†**
LF(ms^2)	388+/_62.5(8)	98.5+/_28.24(8)	**0.0009†**
HF(ms^2)	200+/_36.23(8)	151+/_58.93(8)	0.484†
LF/HF	1.37+/_0.498(12)	1.246+/_0.349(12)	0.222††
Total power (ms^2)	1402 (+/-) 239.4(8)	672.1(+/-)290.4(8)	**0.02††**

Table 3: Comparison of Frequency domain parameters between right and left stroke.
RH stroke – right MCA stroke, LH stroke – left MCA stroke.
VLF- very low frequency, LF- low frequency, HF- high frequency, LF/HF – ratio signifying sympathovagal balance.
† p value obtained through independent samples t-test to compare the distribution of values between two groups.
†† p value obtained through test to compare the Mann Whitney U- test of values between two groups

Time domain parameter	RH Stroke (n=12) Mean +/_S.E.M(n)	LH Stroke (n=13) Mean +/_ S.E.M(n)	P value
Mean HR	72.5(+/-) 2.318(12)	83.63(+/-) 3.702(13)	0.0242†
RMSSD	29.81(+/-) 4.58(9)	24.33(+/-) 4.516(12)	0.4133†
SDNN	36.75(+/-) 5.09(8)	27.14(+/-) 3.828(10)	0.143††
NN50	10.11(+/-) 3.09(11)	24.61(+/-) 5.355(10)	0.009††
PNN50	5.57(+/-) 1.64(10)	4.5(+/-) 1.364(13)	0.62†

Table 4: Comparison of Time domain parameters between right and left stroke.
RH stroke – right MCA stroke, LH stroke – left MCA stroke.
RMSSD – the root mean square of successive differences of NN interval
SDNN – successive deviation of NN intervals
NN50 – the number of successive NN intervals that differ by more than 50 ms.
PNN50 – the percentage of successive NN intervals that differ by more than 50ms.
†p value obtained through independent samples t test
†† p value obtained through Mann Whitney U test to compare the distribution of values between two groups

Non-linear results	RH Stroke (n=12) Mean +/_ S.E.M(n)	LH Stroke (n=13) Mean +/_ S.E.M(n)	P value
SD1	32.09 +/- 11.99(8)	28.26 +/- 8.295(10)	0.761††
SD2	91.93+/- 21.18(10)	40.68+/- 8.14(11)	**0.031**†
Shannon entropy	3.023 +/- 0.136	3.498 +/- 0.118	**0.016†**
Sample entropy	1.25 +/- 0.09	1.24 +/- 0.16	0.865††

Table 5: Comparison of Non linear measures between right and left stroke.

SD1 – instantaneous beat to beat R-R interval variability

SD2 – long term continuous R-R interval variability

† P value obtained through independent samples t test.

††P value obtained through Mann Whitney U test to compare the distribution of values between two groups.

Ewing's Autonomic failure classification	LH stroke (n=12)	RH stroke(n=12)	P value
	n (%)	n (%)	
Normal	7(58.3%)	5(41.66%)	0.640†
Early	1(8.33%)	1(8.33%)	
Definite	2(16.7%)	2(16.7%)	
Severe	1(8.33%)	1(8.33%)	
Atypical	1(8.33%)	3(25.0%)	

Table 6: Comparison of Ewing's Autonomic Failure classification between right and left stroke.

RH stroke – right MCA stroke, LH stroke – left MCA stroke.

Percentages are column-wise

† P value obtained through Fisher's exact test

Discussion

Previous studies have shown deranged cardiac autonomic tone long after the stroke, i.e. up to 9 months after the index event [16]. In earlier studies Power spectrum of H.R.V was found to be related to stroke severity. There was a significantly linear correlation between H.R.V and stroke severity [13]. LF/HF ratio correlated negatively with stroke severity scores in modified National Institute of Health Stroke Scale (mNIHSS) [17]. Due to the fact that in our study the subjects were comparable in terms of severity of stroke these factors may have played a minimum role in the outcome of the autonomic parameters.

From animal and human studies it is well established that there are asymmetries in autonomic innervations of the heart. Experimentally, right cerebral hemisphere has been shown to modulate sympathetic activity [24]. Barron et al. reported that cardiac parasympathetic tone was reduced after right and left stroke with a greater reduction in the right side within 4 to 11 days after stroke [1]. Takzogulu et al. demonstrated a more profound decrease in H.R.V when right middle cerebral artery and insula were affected in acute ischemic stroke studied immediately after admission for stroke [26]. In this cross – sectional study subjects with Right MCA stroke demonstrated a higher sympathetic dominance after 3 – 4 months of stroke. Whether this is primarily due to a stroke or a compensatory response needs to be further studied.

In short term HRV recordings after stroke VLF, LF and Total Power could be the most important parameters among the linear indices. In our study all the three parameters were significantly higher on the right side, VLF (p=0.005), LF (p= 0.0009) and Total Power (0.02). Previous studies have confirmed that all these parameters are reduced in stroke patients when compared to healthy controls [16]. Thus there is a clear sympathetic dominance after right MCA stroke. It is suggested that right middle cerebral artery infarction disinhibits insular function, resulting in increased sympathetic cardiovascular tone and the cardiac consequences of stroke [21]. Meyer and colleagues reported that patients with right hemispheric stroke involving the insular cortex are more susceptible to develop cardiac autonomic dysfunction [18]. To further strengthen their findings Colivicci et al. reported that right insular cortex was associated with more complex arrhythmias [4]. Oppenheimer too demonstrated disturbed cardiac autonomic tone after left insular cortex stroke. The higher Total power after right MCA stroke could be due to the contribution of LF. The higher HF on the right side though not significant may be due to a vagal compensation or due to the loss of cortical inhibition on the vagal nuclei. Previous studies have shown medullary brainstem infarction seems to cause both sympathetic and parasympathetic dysfunction, which may contribute to the occurrence of cardiac complications in stroke [12]. In line with the results from our study Dutsch et al. demonstrated an increased sympathetic cardiovascular modulation 18-43 months after RH lacunar stroke [5].

The time domain analysis of short term ECG recordings does not correlate well with the frequency domain parameters and with the previous studies which mainly used 24 hour recordings. How-

ever the role of RMSSD needs to be investigated further as a higher RMSSD may reflect a parasympathetic compensation predominantly on right so as to balance the higher sympathetic tone. In this regard the higher HF and RMSSD i.e. a higher parasympathetic tone after right M.C.A stroke could explain the significantly lower heart rate on the right side (P=0.024). It is well established that the heart rate is predominantly under the parasympathetic control.

Only one study earlier has reported non linear HRV measure after stroke [22]. In this study Oppenheimer showed that randomness is reduced significantly after left insular stroke. In our study we found SD2 and Shannon entropy as a valuable and sensitive indicator of difference between the two groups. The higher Poincare SD1 and SD2 (p= 0.031) measures have been shown to reflect a higher randomness in the heart beats and thus an increased risk for ventricular arrhythmias and sudden death. Lower Shannon entropy was also significant after right stroke (p=0.016).

The clinical non invasive reflex cardiac tests both sympathetic and parasympathetic were not significantly different between the two groups (P= 0.64). Naver., *et al* [20] also showed that peripheral reflexes are same between left and right stroke.

So in conclusion we can say that immediately after a stroke there is an increase in the sympathetic tone due to disnhibition of the sub cortical centres. This may be more predominant on the right side. After a few months there is a vagal compensation and hence the sympathovagal balance returns towards normal. While the authors feel the prognostic value of time domain analysis from short term ECG recordings in chronic stroke (3-4 month period) is limited, future research has to focus on frequency domain measures and non linear variables. HRV can certainly provide insight into the pathophysiology of cardiac autonomic imbalance after stroke. Future studies will also have to incorporate functional MRI to quantify and precisely localise specific cortical areas responsible for autonomic dysfunction.

Conflict of Interest

On behalf of all authors the corresponding author states that there is no conflict of interest.

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