SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

AUTONOMIC DYSFUNCTION IN FIRST EVER ISCHEMIC STROKE: PREVALENCE, PREDICTORS, SHORT TERM NEUROLOGICAL AND CARDIOVASCULAR OUTCOME-A PROSPECTIVE STUDY

Thesis submitted in partial fulfillment of the rules and regulations for

DM Degree Examination of

Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

Dr.Sandeep Nayani

DM Neurology Resident

Month and Year of Submission: October 2014

Department of Neurology
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Thiruvananthapuram

2012-2014

DECLARATION

I, **Dr.Sandeep Nayani**, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram **Dr.Sandeep Nayani**

Date:

Forwarded

The candidate, Dr. Sandeep Nayani, has completed the project under my guidance.

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Date:

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ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to **Dr.Sapna Erat Sreedharan**, Assistant Professor of Neurology, SCTIMST, my guide for the study, for her expert guidance, constant review, kind help and keen interest at each and every step of the study

I am thankful to **Dr.M.D.Nair**, Professor and Head, Department of Neurology for his guidance, encouragement and valuable suggestions during the period of the study.

I am thankful to **Dr.P.N.Sylaja**, Additional Professor and in-charge of Comprehensive Stroke program, Department of Neurology for her keen interest, guidance and support for the completion of study.

I express my gratitude to **DrNarayanan Namboodiri K.K**, Additional Professor, Department of Cardiology, SCTIMST for his guidance.

I express my sincere thanks to **Dr.Sankara Sarma**, Professor, AchuthaMenon Centre for Health Science Studies for helping me with the statistical analysis of this study.

I am extremely thankful to the medico-social workers, nurses, technicians and my colleagues in the Department of neurology and cardiology for their valuable input and assistance to the study.

I extend my gratitude to all my patients and their primary caregivers who willingly participated in this study.

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INTRODUCTION

Stroke is the third most common cause of disability among people over the age of 65 years. Globally, stroke is the second leading cause of death .Initial severity of stroke and age are currently considered the most powerful predictors of functional recovery and eventual home discharge of ischemic stroke survivors.

Considerable evidence has been collected over the past 20 years suggesting that acute stroke may determine a major derangement of cardiovascular function. In particular, an impairment of the autonomic balance and an increased incidence of cardiac dysrhythmias have both been noted.

Stroke has been shown to produce changes in autonomic function, increase the incidence of cardiac arrhythmias, cause myocardial damage, and raise plasma catecholamine levels. The most important consequence of these changes is an increased susceptibility to sudden death. The crucial control sites of the autonomic function are found to be the insular cortex, amygdala, and lateral hypothalamus. In addition, evidence exists for cortical asymmetry in the regulation of cardiovascular functions. Autonomic dysfunction may be an indicator of severity of stroke. Increasing stroke severity was associated with progressive loss of overall autonomic modulation, decline in parasympathetic tone, and progressive shift toward sympathetic dominance. Autonomic dysfunction may predispose not only to adverse cardiovascular outcomes, but also poor neurological recovery.

There is no literature regarding prevalence of autonomic dysfunction in Asian population of stroke survivors. Also there is scant literature regarding predictors of

autonomic dysfunction as well as its influence on neurological recovery in ischemic stroke.

We sought to the prevalence of autonomic dysfunction in patients with first ever acute ischemic stroke, predictors of autonomic dysfunction in hemispheric strokes like hemispheric laterality, cortical location of infarct, severity of stroke, age and the short term outcome in patients with and without autonomic dysfunction.

REVIEW OF LITERATURE

Autonomic dysfunction in Stroke

It is well known from animal and clinical studies that cerebrovascular diseases can alter cardiovascular and autonomic function. Stroke has been shown to produce changes in autonomic function, increase the incidence of cardiac arrhythmias and cause myocardial damage[(1)]. The most important consequence of these changes is an increased susceptibility to sudden death[(2).] In patients with acute stroke, the incidence of sudden death as a result of arrhythmic causes has been reported to be 6% in first 48 hours. 1 year fatality of ischemic stroke is around 31%,with half of the mortality secondary to cardiovascular events[(3).]From the Dutch TIA Trial Study, sudden death accounted for 43% of serious cardiac events (death or nonfatal myocardial infarction) during long-term follow-up of patients after transient ischemic attack or minor stroke[(4)]

Animal and human research has shown that autonomic dysfunction is common after acute stroke. One of the recent studies have noted that around 75% of acute stroke patients have autonomic impairment. [(1)] Autonomic dysfunction, among other factors, is evident in impaired physiological regulation of heart rate and blood pressure, and in increased secretion of catecholamine and cortisol. Autonomic imbalance might contribute not only to the development of fatal and non-fatal arrhythmias, but also to myocardial injury.

The physiological variability of the heart rate—the variation of the interval between consecutive heartbeats over time—is indicative of the heart's ability to adjust to circulatory changes and serves as an important parameter for the assessment of

autonomic functions. Several investigators have reported decreased heart rate variability in patients with stroke, which is found not only in the acute phase, but also 1 month and 6 months after the event. The baroreflex is the principal mechanism to ensure stability of heart rate and blood pressure during changes of body position. Baroreflex sensitivity is reduced in patients with acute and sub-acute stroke[20]. Impaired baroreflex sensitivity is associated with long-term mortality after acute ischemic stroke[14].

Pathophysiology of Autonomic dysfunction in Hemispheric Stroke

Cardiac autonomic innervation originates in brain stem (parasympathetic) and spinal (sympathetic) nuclei. An anatomic basis for cerebral hemispheric influences on autonomic function is provided by projections onto autonomic nuclei from cortical, amygdaloid, hypothalamic, and limbic structures. Cerebral infarction presumably reduces cardiac autonomic innervation by removal of ipsilateral suprasegmental stimulation of the primary autonomic nuclei[51].

The central nervous system controls cardiac activity and vasomotor tone by a complex system of cardiovascular reflexes that regulate cardiac performance to meet the demands of the body even in rapidly changing circumstances. The reflex arc consists of three parts: the afferent autonomic pathway, the medullary and hypothalamic processing centers, and the sympathetic and parasympathetic efferent pathways.

The sympathetic nervous system facilitates cardiac activity by increasing HR and contractility, whereas the parasympathetic nervous system has an inhibitory effect on the heart. The autonomic cardiovascular regulatory system operates by continuously

balancing the sympathetic and parasympathetic system[40]. In addition to the basal brain structures, the cerebral cortex is also involved in the regulation of cardiac and vasomotor activity via the hypothalamus; thus, for example, emotional stress may cause excitation of the cardiovascular system.

The role of the parasympathetic nervous system in producing cardiovascular disturbances in brain infarction is not as clearly defined as that of the sympathetic system. Experimental stimulation of the medullary cardio inhibitory neurons in the nucleus ambiguus, dorsal vagal nucleus, anterior and preoptic hypothalamic regions, orbitofrontal cortex, and insular cortex has evoked bradycardia and hypotension. Moreover, prolonged phasic stimulation within rat insular cortex resulted in atrio-ventricular and interventricular heart block, QT interval prolongation, ventricular ectopy, and death. In humans, Oppenheimer et al recently demonstrated that stimulation of the left insular cortex produces bradycardia, and stimulation of the right insular cortex produces tachycardia[22].

The pathophysiologic basis of the cardiovascular autonomic dysregulation associated with focal cerebral lesions is not completely understood. The observed abnormalities may result from damage to the cortical or subcortical structures or to the neural pathways known to regulate the cardiovascular autonomic system or they may be related to various neuro-humoral consequences of cerebral lesions. The insular cortex, lying within the middle cerebral artery territory, is the most important cortical area, controlling both sympathetically and parasympathetically mediated cardiovascular regulation. It has extensive connections with the other autonomic regulatory areas

located in the subcortical limbic and forebrain regions, but the pathways linking it with the cardio regulatory centers have not been established in detail[39].

Predictors of Autonomic dysfunction in Stroke

Several factors were found to play role in incidence of autonomic dysfunction after hemispheric stroke. There are several studies on influence of stroke severity, hemispheric lateralization, insular involvement and stroke subtype on incidence of autonomic dysfunction after hemispheric strokes. Some of these studies had conflicting results, particularly with respect to hemispheric lateralization of autonomic dysfunction.

Some authors have also suggested a possible effect of carotid bulb involvement in development of post stroke autonomic dysfunction [10], an observation which has not had many supporters [36].

Stroke severity and Autonomic Dysfunction

Autonomic dysfunction may be an indicator of severity of stroke. Increasing stroke severity was associated with progressive loss of overall autonomic modulation, decline in parasympathetic tone, and baroreflex sensitivity, as well as progressive shift toward sympathetic dominance. All autonomic changes put patients with more severe stroke at increasing risk of cardiovascular complications and poor outcome. NIHSS scores has been used to predict risk of autonomic dysregulation in some studies [11]

Progressive loss in autonomic modulation in patients with more severe stroke also causes deteriorating heart rate and BP adjustment to instantaneous changes of either parameter because of declining baroreflex sensitivity. Sykora et al[36] showed that baroreflex sensitivity impairment depends on the volume of the stroke and involvement of the insula; they confirm the conclusions of Robinson et al[14] that baroreflex sensitivity deterioration after stroke reflects central autonomic dysfunction. Studies by Sykora et al and Hilz et al[11,40] found correlations between decreasing baroreflex sensitivity and increasing NIHSS scores.

Hemispheric Laterality and Autonomic dysfunction

In clinical and experimental studies, evidence exists for cortical asymmetry in the regulation of cardiovascular functions. Cardiac abnormalities seem to be more frequent in patients with right-sided strokes, whereas concurrent insular damage may further impair autonomic function and constitute, at least in the acute phase, increased risk of adverse cardiovascular events[5,6,7]

However some authors have published conflicting results. NASCET group[8] found that left-sided, not right-sided, brain infarction is associated with increased risk of sudden death. Left-handed or ambidextrous patients have a lower risk of sudden death than right-handed patients, suggesting a role for lateralization of autonomic function. Vista investigators found that there was no difference in functional outcome between patients with right or left hemisphere stroke. Stroke lateralization is not an important predictor of cardiac adverse events or 90-day mortality[9].

There are many reports about differences in autonomic dysfunction after left- and right-sided stroke. Although many studies found a shift toward more prominent sympathetic modulation after right-hemispheric stroke, there are also reports that only found a decrease in total autonomic modulation or a decrease in parasympathetic outflow after right-hemispheric stroke. Moreover, NIHSS scores are higher with left-sided than with right-sided stroke. Hemispheric predominance of autonomic modulation might account for discrepancies of autonomic dysfunction and of its correlation with NIHSS scores between patients with right and left middle cerebral artery stroke[2, 5,6,8].

Differential effects on autonomic functions have been noted after unilateral inactivation of the cerebral hemispheres by intracarotid amobarbital. Inactivation of the left hemisphere resulted in increased heart rate and blood pressure compared with these measures before inactivation. By contrast, a decrease in heart rate was reported after right-hemispheric in activation. Similarly, the effects of experimental ischemic infarcts after occlusion of the left or right middle cerebral arteries suggest a lateralization of autonomic functions. Through the integration of the concepts of hemispheric specialization of autonomic control and the key role of the insular cortex, substantial efforts have been made to investigate the distinct functions of the left and right insulae. A widely acknowledged model of insular specialization entails the right insula as the Centre for sympathetic autonomic control and the left insula as the Centre for parasympathetic control[25,26].

Stroke Localization and Autonomic Dysfunction

Traditionally, research on the central control of cardiac functions focused on autonomic circuits at the spinal and brainstem level. More recently, several lines of experimental and observational evidence have suggested that a widespread cortical and subcortical network, including the bilateral insular cortex, anterior cingulate gyrus, amygdala, and hypothalamus, is involved in the central control of the autonomic nervous system[(15)].

The insulae—areas of polymodal sensory, cognitive, and affective integration—are regarded as a crucial part of this network. The insular cortex is involved in processing somatosensory and nociceptive stimuli and in the control of voluntary and semi-voluntary movements, such as speech production and swallowing.

Lesions of the insular cortex or the sub-insular white matter are associated with alterations in autonomic tone, resulting in impaired control of blood pressure and heart rate, and ultimately life-threatening cardiac arrhythmias. A detailed understanding of the central control of the autonomic nervous system, particularly the insulae, will increase the predictive power of brain imaging to identify patients at high risk of sudden death after stroke [(7)].

Changes in heart rate and blood pressure following insular stimulation or lesions in animal models as well as in humans are well documented. Electrocardiographic (ECG) abnormalities are frequent in acute stroke. The mechanism by which these abnormalities occur is not well understood but may involve the insular cortex; insular damage may cause activation of the sympathico–adrenal system because of decreased inhibitory insular activity. Intraoperative insular cortex stimulation is suggestive of right sided dominance in mediation of sympathetic cardiovascular effects, and

subarachnoid haemorrhage in the right sylvian fissure has been shown to have cardiac consequences. These findings have been supported by animal models, leading to the hypothesis that insults to the right insula in a direct or indirect manner affect cardiac function; a possible consequence may be sudden cardiac death after stroke[24,26].

Insular cortex stimulation in rats results in EKG repolarization changes and cardiac arrhythmias associated with elevation of plasma norepinephrine levels and myocardial damage. Patients with insular infarction had a significant nocturnal blood pressure "rise" and higher norepinephrine levels than those with strokes in other cortical locations, suggesting increased sympathetic activity. In addition, insular infarction was associated with QTc prolongation and an increased incidence of ventricular arrhythmia [22,28].

In humans, right anterior insular stimulation during surgery increased sympathetic cardiovascular responses whereas left insular stimulation resulted in cardiovascular parasympathetic effects. Finally, left insular cortex lesions increase basal cardiac sympathetic tone and decrease randomness of heart rate variability. Stroke-induced left insular damage might therefore shift cardiac autonomic balance toward sympathetic predominance, which may alter cardiac rhythm and wall motion [21].

Research on the consequences of insular lesions is complicated by the fact that most insular lesions are part of a larger infarct in the distribution of the middle cerebral artery. Ischemic lesions limited to the insular cortex are rare. A few case reports on patients with isolated insular lesions suggest that hemorrhagic or ischemic infarcts of the right insula can lead to marked bradycardia and recurrent asystole. These findings support the notion that a right insular lesion decreases sympathetic tone and results in parasympathetic overactivity. Conversely, lesions confined mainly to the left insula

increased basal cardiac sympathetic tone and were associated with a decrease in heart rate variability[29,30].

By contrast, right insular lesions might also be associated with hypertension and tachycardia. In patients with stroke, pathological activation of the sympathetic nervous system was noted after insular lesions of either hemisphere, but occurred more frequently after right hemisphere insular infarcts.

Conflicting evidence for the localization of sympathetic and parasympathetic centres in the insulae might arise because of inter-individual differences in insular lateralisation—eg, related to handedness. Left-handed or ambidextrous patients with a transient ischemic attack or a minor stroke due to symptomatic carotid disease had a lower risk of sudden death than right-handed patients. In addition to the insulae, the anterior cingulate cortex seems to be a major component of the central autonomic network[37,47]. Because ischemic infarcts occur less frequently in the anterior cerebral artery than in the middle cerebral artery territory, the autonomic consequences of anterior cingulate cortex lesions have not attracted marked clinical attention[47].

Autonomic function Testing

There are different testing methods for assessing autonomic function at bedside. Unlike other systems, autonomic function is not typically directly assessed. Instead, responses of complex overlapping reflex loops are measured after controlled perturbations, most commonly of heart rate, blood pressure, and sweating. Some authors have used battery of clinical tests for assessing autonomic function in stroke patients and scored severity of affection using Ewing's classification[1] while a few authors have used heart rate variability measures(HRV) using 24 hour ECG recording

and derived time domain and frequency domain parameters for assessing autonomic dysfunction[2,12].

It is clearly established that abnormal autonomic control, measured by heart rate variability, is an independent predictor of death after myocardial infarction and heart failure.

Bedside Autonomic Function Testing

Bedside Autonomic function testing includes Parasympathetic tests like Valsalva maneuver, Deep breathing test, 30 : 15 ratio of Heart Rate and Sympathetic tests like Orthostatic BP measurement and Sustained handgrip Test[34].

Valsalva maneuver:

The Valsalva maneuver (VM) is a reliable and reproducible method that provides information for both parasympathetic and sympathetic function if beat-to-beat heart rate (HR) and blood pressure (BP) data are recorded. The subject blows into a closed tube at 40 mm Hg for 15 seconds while HR and BP are recorded. A small leak is introduced to prevent maintaining pressure without effort by using a closed glottis. Some feedback is also generally provided to ensure the intended degree of effort. Isolated Valsalva ratio (VR) HR recording requires minimal equipment but more information is gathered with less chance of misinterpretation if continual BP is recorded. The VM blood pressure waveform is divided into 4 distinct phases (I-IV). Phases I and III signify nonspecific transmitted pressure and release from the maneuver, which initially causes cardiac output and BP to drop providing the test stimulus. Normally, peripheral vasoconstriction and increased HR produce partial or full reversal of the BP decline, marking early (BP drop) and late (BP recovery) phase

II. After Valsalva ends the BP slowly overshoots and later returns to baseline (phase IV overshoot).

Adrenergic insufficiency causes phase II to progressively deepen or fail to correct. Phase IV may fail to overshoot. Phase II recovery is likely mediated by _-adrenergic stimulation and phase IV primarily by βadrenergic activity, which is supported by pharmacological studies.12 HR normally increases during the Valsalva period then undershoots below baseline values. The Valsalva ratio (VR) is calculated by dividing the R-R interval of the HR nadir over the HR peak during this period.

Standing, Orthostatic BP and the 30:15 Ratio

Standing initiates a coordinated sequence of reflexes to maintain BP and therefore cerebral perfusion. Simple HR and BP responses to standing are important bedside markers of autonomic integrity, Baseline values are recorded and readings are taken at least every minute for 2 to 5 minutes. Leg muscle contraction necessary for active standing triggers an exercise reflex that transiently reduces BP that can mimic true, sustained orthostatic hypotension. Pressure normally returns to baseline levels within 1 to 2 minutes but recovery can be delayed for 3 to 15 minutes in patients with mild orthostatic intolerance. This phenomenon is why standing BP measures must be delayed. The 30:15 ratio, the R-R interval ratio of the HR nadir around beat 30 after active standing divided by the HR peak near beat 15, is an alternative, parasympathetic function test.

A BP decrease of 20 mm Hg systolic or 10 mm Hg diastolic within 3 minutes is considered significant; triggered symptoms are also noted. patients with other forms

of orthostatic intolerance often have excessive HR increases, commonly defined as a 30 beats per minute increase usually with a rate exceeding 120 beats per minute.

Lab Testing for Autonomic Dysfunction

Measurement of heart rate variability[33]:

HRV may be measured using either Time Domain measures or Frequency Domain measures.

I) **Time Domain Measures**

Variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the time domain measures. With these methods either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous electrocardiographic (ECG) record, each QRS complex is detected, and the so-called normal-to-normal (NN) intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations), or the instantaneous heart rate is determined. Simple time-domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval

From a series of instantaneous heart rates or cycle intervals, particularly those recorded over longer periods, traditionally 24 h, more complex *statistical time-domain measures* can be calculated. These variables may be derived
from analysis of the total electrocardiographic recording or may be calculated using smaller segments of the recording period. The latter method allows comparison of HRV to be made during varying activities, e.g. rest,
sleep, etc.

The simplest variable to calculate is the *standard deviation of the NN interval* (SDNN), i.e. the square root of variance. Since variance is mathematically equal to
total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. In many studies, SDNN is calculated over a 24-h period and thus encompasses both short-term high frequency variations, as well as the lowest frequency components seen in a 24-h period. As the period of monitoring decreases, SDNN estimates shorter and shorter cycle lengths. Therefore, durations of the recordings used to
determine SDNN values (and similarly other HRV measures) should be standardized. Short-term 5-min recordings and nominal 24 h long-term recordings seem to be appropriate options.

The most commonly used measures derived from interval differences include ***RMSSD***, the square root of the mean squared differences of successive NN intervals, ***NN50,*** the number of interval differences of successive NN intervals greater than 50 ms, and ***pNNSO*** the proportion derived by dividing NN50 by the total number of NN intervals. All these measurements of short-term variation estimate high frequency variations in heartrate and thus are highly correlated.

II) **Frequency Domain Measures**

Power spectral density (PSD) analysis provides the basic information

of how power distributes as a function of frequency. Methods for the calculation of PSD may be generally classified as *non-parametric* and *parametric.* In most instances, both methods provide comparable results. Three main spectral components are distinguished in a spectrum calculated from shortterm recordings of 2 to 5 min: very low frequency (VLF), low frequency (LF), and high frequency (HF) components. The distribution of the power and the central frequency of LF and HF are not fixed but may vary in relation to changes in autonomic modulations of the heart period. Measurement of VLF, LF and HF power components is usually made in absolute values of power (ms2).

Outcome in patients with Autonomic dysfunction after Stroke

Recently some authors have also found that autonomic dysfunction may predispose not only to adverse cardiovascular outcomes, but also poor neurological recovery. Xiong etal in their series of 34 patients with acute ischemic stroke found that 2 month functional outcome of those with severe autonomic dysfunction was poor when compared to those with mild autonomic dysfunction[(1).]

There is only scant literature regarding short and long term neurological outcome patients with autonomic dysfunction. A recent study by Xiong etal [(1)] found 2 month functional outcome to be poor in stroke survivors with autonomic dysfunction. Also none of the studies have systematically assessed the effect of stroke severity, cortical

versus subcortical location of infarct and etiology of stroke with autonomic function impairment in stroke patients and correlated it with neurological and cardiovascular outcomes at short and long term.

Fatality rates 1 month after stroke are high, 23% for all-cause stroke. Long-term mortality is also higher than the general population with >2-fold relative risk of death for those surviving beyond 30 days. The majority of deaths beyond 30 days are caused by nonstroke-related events, in particular cardiac death.2 One-year fatality rate is 31% for cerebral infarction and 37% for all-stroke cause[43].

Short and long term followup of stroke patients with autonomic dysfunction have shown increased adverse cardiac events. Robinson's study [14] reported that reduced baroreflex sensitivity in the acute stroke phase was an independent predictor for all-cause mortality during a median 4-year follow-up. Another study of 84 stroke patients found abnormal heart rate dynamics, measured immediately after stroke, was the only independent predictor of all-cause mortality over 7-year follow-up[12] .In another study of 62 patients with acute ischemic stroke, 7 patients who experienced sudden death had a significantly reduced time domain measure of heart rate variability and a trend toward reduced low-frequency spectral power compared with survivors.[15]

The annual cardiac mortality after stroke (5 to 10%) represents the single most common cause of death on long-term follow-up. Accumulating evidence suggests that this mortality may not be entirely explained by concomitant coronary artery disease: cerebral injury may directly contribute to the generation of cardiac dysfunction. Acute stroke has been associated with a pattern of increased serum cardiac enzymes and EKG repolarization changes that are not typical of ischemia. The

reported association between cardiac arrhythmia and rise in serum cardiac enzyme levels at stroke onset may indicate an acute myocardial lesion related to brain injury in some cases, rather than the converse phenomenon. A particular form of cardiac necrosis termed myocytolysis has been identified in patients who have died after stroke; these changes can be seen with normal coronary arteries and are focused on intracardiac nerves rather than blood vessels, indicating a possible neural origin. The nature of the nerves involved is unclear but plasma norepinephrine may be elevated after stroke and associated with functional cardiac alteration in experimental models indicating a sympathetic neural association. In this regard, patients with stroke with higher mean plasma norepinephrine concentration show higher CK values, suggesting cardiac damage from activated sympathetic tone.

A likely clinical correlate to myocytolysis, neurogenic stunned myocardium, a phenomenon of reversible globally diminished myocardial wall motion in association with acute neurologic events, has been reported after acute stroke and subarachnoid hemorrhage. Massive intracardiac neural release of catecholamines may be the underlying mechanism, again indicating sympathetic involvement. In an experimental stroke model, cats with myocytolysis had a significant elevation of plasma norepinephrine compared to cats without myocardial damage. These data indicate that stroke- related cardiac damage likely arises from a shift of autonomic function toward augmented cardiac sympathetic tone[(50)].

HYPOTHESIS AND OBJECTIVES OF THE STUDY

HYPOTHESIS

Acute ischemic Stroke is associated with high incidence of autonomic dysfunction. Patients with Autonomic dysfunction after acute ischemic stroke have poorer outcome compared to patients without Autonomic dysfunction.

OBJECTIVES

1) To study the prevalence of autonomic dysfunction in patients with first ever acute ischemic stroke.

2) To study predictors of autonomic dysfunction in hemispheric strokes like hemispheric laterality (side of stroke), cortical location of infarct, insular involvement, severity of stroke, age and risk factors

3) To study the 3-month and 1-year neurological and cardiovascular morbidity and mortality in patients with and without autonomic dysfunction

SUBJECTS AND METHODS

Study design and setting:

The study was a hospital based Prospective study. The subjects were selected from among the patients attending the Neurology outpatient clinic, Stroke outpatient clinic and in-patients admitted in Stroke Intensive Care Unit of a single tertiary centre (Sree Chitra Institute of Medical Sciences and Technology, Thiruvananthapuram).

Study period:

The study was conducted over a period of 24 months from April 2012 to March 2014.

Methodology:

Consecutive patients with hemispheric Stroke within 3 months with imaging showing an acute/sub-acute infarct were screened for eligibility for the study. Those fulfilling the inclusion and exclusion criteria were explained the procedure and those willing to give informed consent were recruited into the study.

Data regarding demographic characteristics, risk factors, medication use and previous history of autonomic symptoms were collected from patient/ bystanders. All the patients underwent investigation for etiology of stroke and vascular risk factors as per standard protocol-including Blood investigations (FBS/PPBS/HbA1C/ FLP/ RFT/ LFT/ Electrolytes), Cardiac evaluation-ECG,2D Echo and Vascular imaging-CT/MR angiogram/ neck vessel Doppler. Stroke severity at presentation was assessed by the National Institutes of Health Stroke Scale (NIHSS) and global disability by the

modified Rankin Scale (MRS). Etiology of stroke was classified according to the modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria[16]

In addition, all patients underwent autonomic function testing using a battery of clinical testing and 24 hour Holter analysis 1 week to 3months from the ictus.

Ethical considerations:

The study was approved by the Institute Ethical Committee. Written informed consent was obtained from all the subjects participating in the study. The informed consent procedure was done according to the guidelines provided.

Inclusion criteria

Patients included in the study fulfilled all the following criteria:

(i) age > 40 years old;

(ii) First ever acute ischemic stroke after 1 week and upto 3months.

(iii) CT or magnetic resonance imaging (MRI) showing cerebral infarct.

(iv) Able to give informed consent.

Exclusion criteria

1. Brainstem stroke.
2. Any clinically relevant arrhythmias on admission, including atrial fibrillation.
3. Any major concurrent illness including severe chronic obstructive pulmonary disease, decompensated cardiac failure, renal failure and malignancies
4. Hypoxia, alterations in consciousness, or any relevant hemodynamic compromise on admission.

5. Diabetes mellitus with evidence of neuropathy
6. Severe strokes with NIHSS>25, those patients requiring decompressive surgery.
7. Imaging negative TIA and minor strokes.

Clinical tests to assess autonomic function[34]:

Tests for Parasympathetic function:

HR response to deep breathing: Heart rate (HR) variability is simple to record and measures are sensitive indicators of parasympathetic function. Cyclic deep breathing is the best validated stimulus; both afferent and efferent pathways are vagally mediated and blunted by anticholinergic agents. The simplest measures are an average of the range of HR change during the test or an average ratio of the minimal to maximal R-R interval differences (E:I ratio).

Valsalva maneuver: Valsalva maneuver (VM) is a reliable and reproducible method that provides information for both parasympathetic and sympathetic function if beat-to-beat heart rate (HR) and blood pressure (BP) data are recorded.HR response to valsalva maneuver or valsalva ratio measures integrity of parasympathetic system whereas BP response during late phase II and phase IV measures adrenergic system.

30:15 ratio: The 30:15 ratio, the R-R interval ratio of the HR nadir around beat 30 after active standing divided by the HR peak near beat 15, is another bedside test for parasympathetic function.

Tests for Sympathetic function:

1. Orthostasis: A BP decrease of 20 mm Hg systolic or 10 mm Hg diastolic within 3 minutes is considered significant; triggered symptoms are also noted.

2. Sustained handgrip – This is performed by having the participant holding the handgrip with 30% of maximal grip for 5 min. Change in diastolic BP was calculated as the difference between the maximal diastolic BP before releasing the handgrip and the mean diastolic BP for the 20 beats immediately prior to handgrip.

Autonomic dysfunction was classified as per Ewing classification as [10,17]

(1)Normal: all tests normal or one borderline

. (2) Early: one of the three heart rate tests abnormal or two border-lines.

(3) Definite: two or more of the heart rate tests abnormal.

(4) Severe: two or more of the heart rate tests abnormal plus one or both of the blood pressure tests abnormal or both borderlines.

(5) Atypical: any other combination.

24 hour Holter monitoring[1]:

24 hour cardiac monitoring was done using 3 channel holter monitor (Seer light/Seer MC, GE electricals Inc.) with commercially available software for measuring time and frequency domains of HRV.

For each recording, the following data were considered:

1. Maximal and minimal heart rate (HR);

2. Total number of premature ventricular contractions (PVC);

3. Presence of ventricular couplets (VC);

4. Presence of episodes of nonsustained ventricular tachycardia (NSVT, 3 or more consecutive PVC);

5. Total number of premature supraventricular contractions (PSVC);

6. Presence of episodes of supraventricular tachyarrhythmias (SVT), including atrial tachycardia and atrial fibrillation

7. Time domain measures - Time domain measures of HRV, includes standard deviation of all normal-to-normal (SDNN) RR intervals and root mean square of differences of adjacent normal-to-normal (rMSSD) RR intervals, were obtained by using the continuous data for 24 hours. SDNN value < 70 msec was predefined as abnormal.

8. Frequency domain measures: Fast-Fourier transform method is used to estimate the power spectrum densities of HR variability. The power spectra were quantified by measuring the areas in the following frequency power bands: <0.0033 Hz (ultra low frequency [ULF]), 0.0033 to 0.04 Hz (very low frequency [VLF]), 0.04 to 0.15 Hz (low frequency [LF]), 0.15 to 0.40 Hz (high frequency [HF]) and HF/LF ratio, as recommended by the task force.

SDNN, rMSSD, and the HF component of HRV correlate with respiratory rhythm and have generally been considered as measures of parasympathetic tone, whereas the LF component correlates with peripheral vasomotor activity and thermoregulation, representing both parasympathetic and sympathetic influences. The LF/HF ratio appears to be an accurate marker of the shifts in sympathovagal balance.[18]

All the patients were followed up at 3 months from the index event. Neurological and functional recoveries were assessed using NIHSS and modified Rankin scale. Any arrhythmias/acute coronary events or recurrent neurological events were elucidated through interview with verification from medical records.

Statistical analysis

The data was analysed using SPSS version 17 software(SPSS Inc,Illinois,Chicago).The descriptive statistics were expressed in means and percentages. Fisher's exact test and chi square test were used to test significance of association between variables. p values less than 0.05 was taken as significant.

Results

Demographic data

Age:

Among the 101 subjects 62(61.4%) were above 60years of age and 39(38.6%) were below 60years of age.

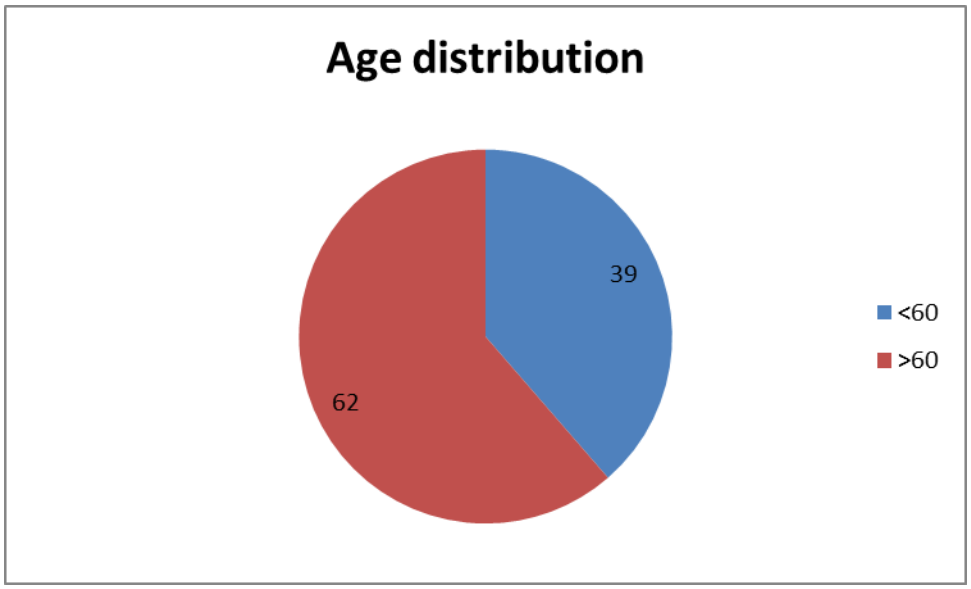
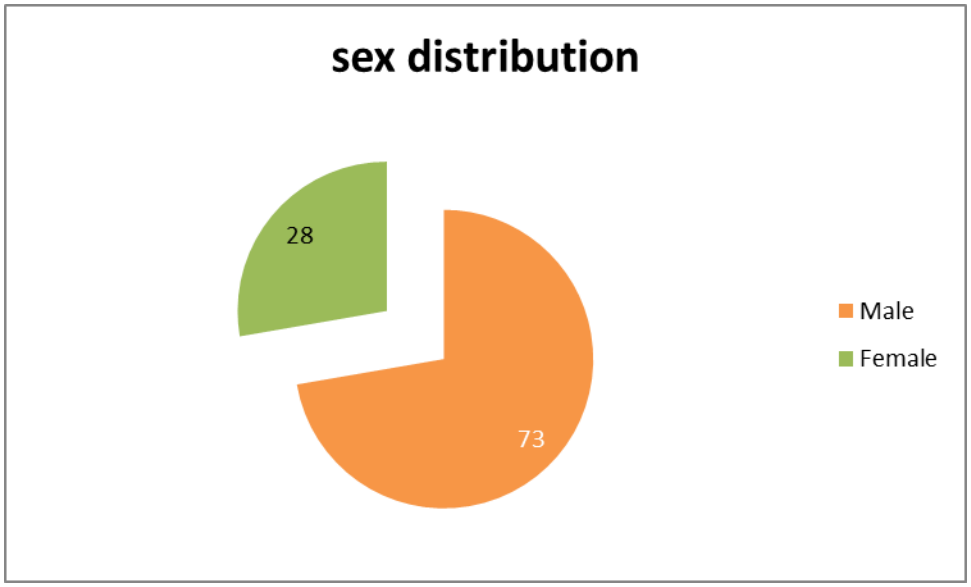


Chart 1: Pie chart indicating number of patients with Age less than 60 years and more than 60 years

Gender: Among the subjects 73(72.3%) were males and 28(27.7%) were females.



Pie chart indicating number of men (orange) and women (green) in study

Risk factors:

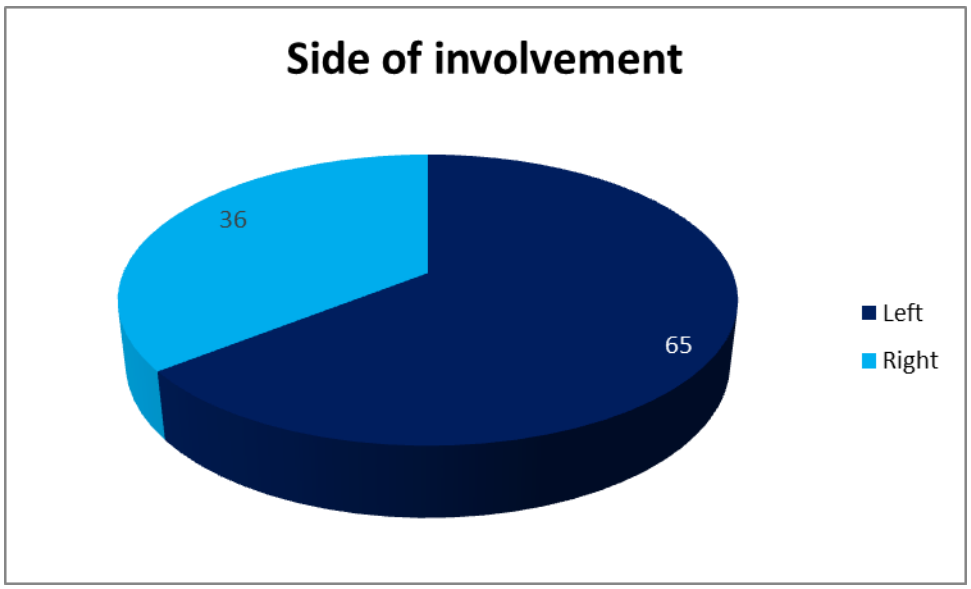
Systemic hypertension was seen in 65 (64.5%) patients, diabetes in 31(30.7%) patients, coronary artery disease was present in 24 (23.8%) patients and dyslipidemia in 9 patients (8.9%). 40 patients (39.6%) were current or reformed smokers.

Risk Factor	Number of Patients	Percent
HYPERTENSION	65	64.4
DIABETES	31	30.7
SMOKING	40	39.6
CORONARYARTERY	24	23.8
DYSLIPIDEMIA	9	8.9

Table: Risk factors of the patients included in study

Side of Stroke involvement:

65 patients (64.4%) had left hemispheric stroke while 36 (35.6%) had right hemispheric stroke



Pie Chart indicating number of patients with left sided and right sided stroke

Stroke Severity at onset:

Out of 101 patients, 20 (19.8%) had mild stroke (NIHSS < 5), 53 (52.5%) had moderate stroke (NIHSS 5-14) and 28 (27.7%) patients had severe stroke (NIHSS > 15)

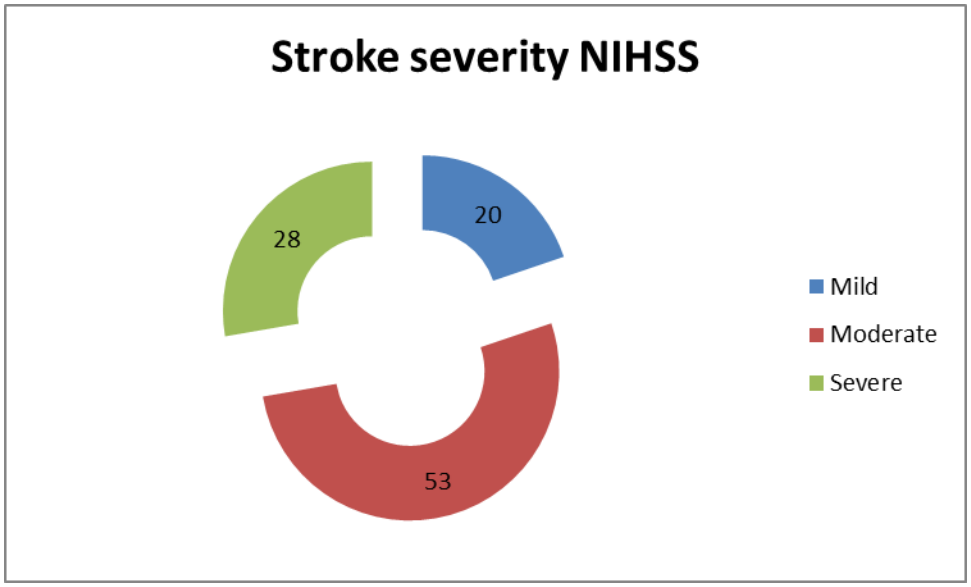


Chart indicating number of patients with mild, moderate and severe stroke (According to NIHSS score)

Infarct Location:

32 patients (31.7%) had infarct in cortical areas, 47patients (46.5%) had subcortical infarcts while 22 patients (211.8%) had both cortical and subcortical infarcts

Stroke Territory	Frequency	Percent
Cortical	32	31.7
Sub cortical	47	46.5
Both	22	21.8
Total	101	100.0

Insular involvement:

24 out of the 101 patients (23.8%) had infarcts involving insular region which is known to be associated with autonomic dysfunction.

INSULAR involvement	Frequency	Percent
Yes	24	23.8
No	77	76.2
Total	101	100.0

Stroke subtype:

Out of 101 patients included in the study, etiology of stroke according to TOAST criteria was Large Artery Atherosclerosis in 30 patients, Lacunar stroke in 33 patients, other known causes in 2 patients (both had carotid dissection) and etiology was undetermined after workup in 36 patients. (Cardioembolic strokes were excluded in our study).

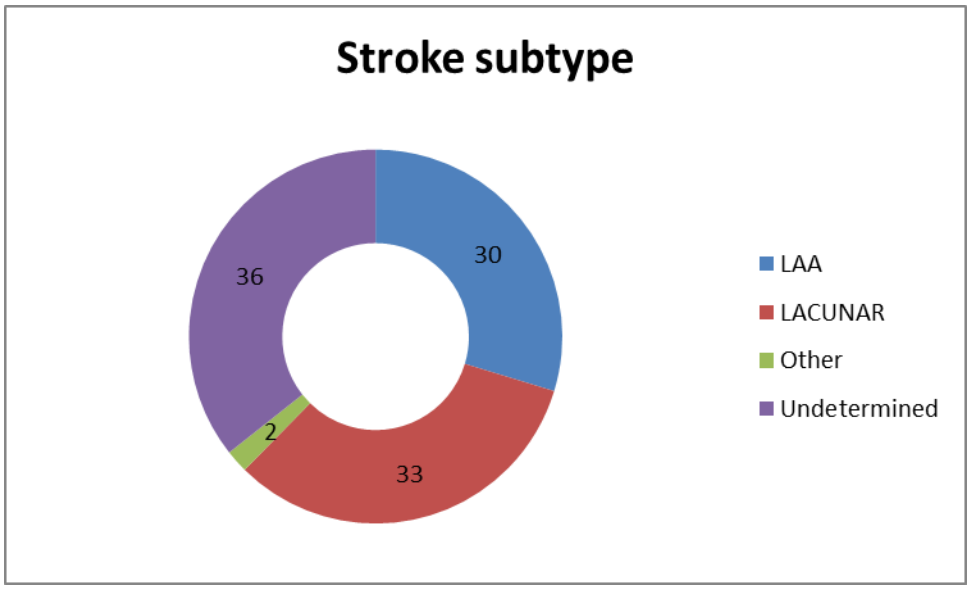


Chart indicating number of patients with different stroke subtypes according to TOAST classification. Cardioembolic strokes were excluded in the study

Vascular complications:

At the time of discharge, 6 out of the 101(5.9%) patients had a new acute coronary event while 4 (4%) patients had a recurrence of stroke while in hospital.

VASCULAR COMPLICATIONS	Frequency	Percent
None	91	90.1
Coronary	6	5.9
Stroke	4	4.0
Total	101	100.0

Stroke outcome:

55 out of 101 patients (54.5%) had good outcome at discharge with mRS<3 while 46 patients (45.5%) had a poor outcome with mRS 4-6

mRS at discharge	Frequency	Percent
0-3	55	54.5
4-6	46	45.5
Total	101	100.0

Incidence of Autonomic dysfunction:

Clinical Autonomic dysfunction: 78 out of 101 patients underwent clinical autonomic function testing. Clinical autonomic battery which included tests of both sympathetic and parasympathetic function was used. 20 out of the 78 patients (25.6%) had evidence of autonomic dysfunction. Patients were classified as per Ewing's

classification[17] of autonomic dysfunction. As per Ewing's classification, 11 patients (10.9%) had early autonomic dysfunction, 6 patients (5.9%) had definite autonomic dysfunction while 3 patients (3%) had atypical autonomic dysfunction.

Clinical Autonomic dysfunction	Frequency	Percent
Yes	20	25.6
No	58	74.4
Total	78	100.0

Ewing classification-Clinical autonomic testing	Frequency	Percent
Could not done	23	22.8
Normal	58	57.4
Early autonomic dysfunction	11	10.9
Definite autonomic dysfunction	6	5.9
Atypical autonomic dysfunction	3	3.0
Total	101	100.0

Holter autonomic dysfunction:

24 hour holter monitoring was done for all patients. Heart rate variability was measured using frequency domain (LF, HF, HF/LF ratio) and time domain (SDNN, rMSSD) measures.

22 out of 101 patients (21.8%) had evidence of autonomic dysfunction.

Holter Autonomic dysfunction	Frequency	Percent
Abnormal	22	21.8
Normal	79	78.2
Total	101	100.0

Comparison of Clinical testing and holter monitoring for Autonomic function testing:

On comparison of clinical testing for autonomic function with holter testing (considered as gold standard), the sensitivity of clinical testing is 38.5 % and specificity was 76.9%. Chi square test showed no significant difference between the two methods for detecting autonomic dysfunction (P=0.30).

			Holter Autonomic dysfunction		
			NO	YES	Total
Clinical Autonomic dysfunction	NO	Count	50	8	58
		% within Clinical_AUTO_DYS	86.2%	13.8%	100.0%
		% within Holter_AUTO_DYS	**76.9%**	61.5%	74.4%
	YES	Count	15	5	20
		% within Clinical_AUTO_DYS	75.0%	25.0%	100.0%
		% within Holter_AUTO_DYS	23.1%	**38.5%**	25.6%
Total		Count	65	13	78
		% within Clinical_AUTO_DYS	83.3%	16.7%	100.0%
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P= 0.30

Predictors of Autonomic dysfunction:

Age, gender and Autonomic dysfunction: The mean age of patients included in our study was 62 years. There was no significant difference between patients with and without autonomic dysfunction with regards to mean age. Age was not found to be a significant predictor of autonomic dysfunction both on clinical autonomic testing (P=0.434) and holter testing (P=0.33).

With regard to gender, 11 out of 58 men (18%) had evidence of autonomic dysfunction on clinical testing while 14 out of 73 men (19%) had evidence of autonomic dysfunction on holter testing. In comparison, 9 out of 20 women (45%) had evidence of autonomic dysfunction on clinical testing while 8 out of 28 females (28.5%) had autonomic dysfunction on holter testing. Though there was increased autonomic dysfunction in females compared to males on clinical autonomic function testing (P=0.021), this was not reproducible on holter testing (P=0.306).

Clinical Autonomic dysfunction	Mean AGE	Number of patients
NO	62.293	58
YES	64.400	20
Total	62.833	78

P= 0.434

Table: Age and Clinical Autonomic dysfunction

Holter Autonomic dysfunction	Mean AGE	Number of patients
NO	62.506	79
YES	64.955	22
Total	63.040	101

P=0.333

Table: Age and Holter Autonomic dysfunction

			Clinical Autonomic dysfunction		
			NO	YES	Total
SEX	Male	Count	47	11	58
		% within Clinical_AUTO_DYS	81.0%	55.0%	74.4%
	Female	Count	11	9	20
		% within Clinical_AUTO_DYS	19.0%	45.0%	25.6%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P= 0.021

Table: Gender and Clinical Autonomic dysfunction

			Holter Autonomic dysfunction		
			NO	YES	Total
SEX	Male	Count	59	14	73
		% within Holter_AUTO_DYS	74.7%	63.6%	72.3%
	Female	Count	20	8	28
		% within Holter_AUTO_DYS	25.3%	36.4%	27.7%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.306

Table: Gender and Autonomic dysfunction on holter testing

Risk factors and Autonomic dysfunction: On comparison of various stroke risk factors with incidence of autonomic dysfunction, none of the traditional stroke risk factors- hypertension, diabetes, smoking, coronary artery disease or dyslipidemia had significant association with autonomic dysfunction, either on clinical testing or on holter monitoring.

			Clinical Autonomic dysfunction		
			No	Yes	Total
HYPERTENSION	No	Count	18	6	24
		% within Clinical_AUTO_DYS	31.0%	30.0%	30.8%
	Yes	Count	40	14	54
		% within Clinical_AUTO_DYS	69.0%	70.0%	69.2%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P=0.93

Table: Hypertension and Clinical autonomic dysfunction

			Holter Autonomic dysfunction		
			No	Yes	Total
HYPERTENSION	No	Count	26	10	36
		% within Holter_AUTO_DYS	32.9%	45.5%	35.6%
	Yes	Count	53	12	65
		% within Holter_AUTO_DYS	67.1%	54.5%	64.4%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.27

Table: Hypertension and Holter autonomic dysfunction

Diabetes:

			Clinical Autonomic dysfunction		
			NO	YES	Total
DIABETES	NO	Count	40	17	57
		% within Clinical_AUTO_DYS	69.0%	85.0%	73.1%
	YES	Count	18	3	21
		% within Clinical_AUTO_DYS	31.0%	15.0%	26.9%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P=0.163

Table: Diabetes and Clinical autonomic dysfunction

			Holter Autonomic dysfunction		
			NO	YES	Total
DIABETES	NO	Count	56	14	70
		% within Holter_AUTO_DYS	70.9%	63.6%	69.3%
	YES	Count	23	8	31
		% within Holter_AUTO_DYS	29.1%	36.4%	30.7%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.514

Table: Diabetes and Holter autonomic dysfunction

Smoking:

			Clinical Autonomic dysfunction		
			NO	YES	Total
SMOKING	NO	Count	34	11	45
		% within Clinical_AUTO_DYS	58.6%	55.0%	57.7%
	YES	Count	24	9	33
		% within Clinical_AUTO_DYS	41.4%	45.0%	42.3%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P= 0.77

Table: Smoking and Clinical autonomic dysfunction

			Holter Autonomic dysfunction		
			NO	YES	Total
SMOKING	NO	Count	46	15	61
		% within Holter_AUTO_DYS	58.2%	68.2%	60.4%
	YES	Count	33	7	40
		% within Holter_AUTO_DYS	41.8%	31.8%	39.6%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.399

Table: Smoking and Holter autonomic dysfunction

Coronary Artery disease:

			Clinical Autonomic dysfunction		
			NO	YES	Total
CORONARY ARTERY DISEASE	NO	Count	47	14	61
		% within Clinical_AUTO_DYS	81.0%	70.0%	78.2%
	YES	Count	11	6	17
		% within Clinical_AUTO_DYS	19.0%	30.0%	21.8%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P= 0.35

Table: Coronary artery disease and Clinical autonomic dysfunction

			Holter Autonomic dysfunction		
			NO	YES	Total
CORONARYARTERY	NO	Count	60	17	77
		% within Holter_AUTO_DYS	75.9%	77.3%	76.2%
	YES	Count	19	5	24
		% within Holter_AUTO_DYS	24.1%	22.7%	23.8%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.897

Table: Coronary artery disease and Holter autonomic dysfunction

Dyslipidemia:

			Clinical Autonomic dysfunction		
			NO	YES	Total
DYSLIPIDEMIA	NO	Count	49	19	68
		% within Clinical_AUTO_DYS	84.5%	100.0%	88.3%
	YES	Count	9	0	9
		% within Clinical_AUTO_DYS	15.5%	0.0%	11.7%
Total		Count	58	19	77
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P= 0.102

Table: Dyslipidemia and Clinical autonomic dysfunction

			Holter Autonomic dysfunction		
			NO	YES	Total
DYSLIPIDEMIA	N0	Count	70	21	91
		% within Holter_AUTO_DYS	89.7%	95.5%	91.0%
	YES	Count	8	1	9
		% within Holter_AUTO_DYS	10.3%	4.5%	9.0%
Total		Count	78	22	100
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.67

Table: Dyslipidemia and Holter autonomic dysfunction

Antihypertensives and autonomic dysfunction: Patients on beta blockers or other antihypertensive medication did not have any difference in incidence of autonomic dysfunction, both on clinical testing and on holter monitoring.

			Clinical Autonomic dysfunction		
			NO	YES	Total
beta_blockers	No	Count	52	20	72
		% within Clinical_AUTO_DYS	89.7%	100.0%	92.3%
	Yes	Count	6	0	6
		% within Clinical_AUTO_DYS	10.3%	0.0%	7.7%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P-0.329

Table: Beta blockers and Clinical autonomic dysfunction

			Holter_ Autonomic dysfunction		
			NO	YES	Total
beta_blockers	No	Count	71	20	91
		% within Holter_AUTO_DYS	89.9%	90.9%	90.1%
	Yes	Count	8	2	10
		% within Holter_AUTO_DYS	10.1%	9.1%	9.9%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.99

Table: Beta blockers and Holter autonomic dysfunction

Side of Involvement: There was no significant difference in incidence of autonomic dysfunction between right sided and left sided strokes, both on clinical autonomic testing (P=0.88) and on holter autonomic testing (P=0.93).

			Clinical_Autonomic dysfunction		
			No	Yes	Total
SIDE_OF_INVOLVEMENT	Left	Count	33	11	44
		% within Clinical_AUTO_DYS	56.9%	55.0%	56.4%
	Right	Count	25	9	34
		% within Clinical_AUTO_DYS	43.1%	45.0%	43.6%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P= 0.88

Table: Stroke lateralization and Clinical autonomic dysfunction

			Holter Autonomic dysfunction		
			No	Yes	Total
SIDE_OF_INVOLVEMENT	Left	Count	51	14	65
		% within Holter_AUTO_DYS	64.6%	63.6%	64.4%
	Right	Count	28	8	36
		% within Holter_AUTO_DYS	35.4%	36.4%	35.6%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.936

Table: Stroke lateralization and Holter autonomic dysfunction

Stroke severity and Autonomic dysfunction: As per NIHSS at admission, all patients were classified as having mild (NIHSS <5), moderate (NIHSS 5-14) and severe stroke (NIHSS 15 or more). We found that patients with milder strokes had lesser incidence of autonomic dysfunction and incidence of autonomic dysfunction increased with increasing severity of stroke. This was found to be highly significant both on clinical autonomic testing (P=0.004) and on holter testing (P=0.001).

Table : Stroke severity at onset and Clinical Autonomic dysfunction			Clinical autonomic dysfunction		
			NO	YES	Total
Stroke_severity_NIHSS	0-4	Count	18	2	20
		% within Clinical_AUTO_DYS	31.0%	10.0%	25.6%
	5-14	Count	39	14	53
		% within Clinical_AUTO_DYS	67.2%	70.0%	67.9%
	>15	Count	1	4	5
		% within Clinical_AUTO_DYS	1.7%	20.0%	6.4%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P=0.004

Table : Stroke severity at onset and Autonomic dysfunction on holter			Holter autonomic dysfunction		
			NO	YES	Total
STROKE SEVERITY: NIHSS SCORE	0-4	Count	18	2	20
		% within Holter_AUTO_DYS	22.8%	9.1%	19.8%
	5-14	Count	46	7	53
		% within Holter_AUTO_DYS	58.2%	31.8%	52.5%
	>15	Count	15	13	28
		% within Holter_AUTO_DYS	19.0%	59.1%	27.7%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.001

Localization & Autonomic dysfunction:

There was no significant difference in incidence of autonomic function based on location of infarct- cortical or subcortical in our study (P=0.52). However, when insular infarcts were studied separately, there was significantly higher incidence of autonomic dysfunction in patients with insular involvement (P=0.003).

Table : Stroke Localization and Clinical Autonomic dysfunction			Clinical autonomic dysfunction		
			NO	YES	Total
STROKE TERRITORY	Cortical	Count	18	6	24
		% within Clinical_AUTO_DYS	31.0%	30.0%	30.8%
	Subcortical	Count	34	10	44
		% within Clinical_AUTO_DYS	58.6%	50.0%	56.4%
	Both	Count	6	4	10
		% within Clinical_AUTO_DYS	10.3%	20.0%	12.8%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P=0.527

Table : Insular stroke and Autonomic dysfunction			Holter AUTONOMIC DYSFUNCTION		
			NO	YES	Total
INSULAR Involvement	No	Count	66	11	77
		% within Holter_AUTO_DYS	83.5%	50.0%	76.2%
	YES	Count	13	11	24
		% within Holter_AUTO_DYS	16.5%	50.0%	23.8%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.003

Stroke subtype and autonomic dysfunction: There was no significant difference in incidence of autonomic dysfunction in different subtypes of stroke, classified according to TOAST criteria. Patients with Large Artery Atherosclerosis, Lacunar strokes, other causes like carotid artery dissections and those with stroke of undetermined etiology had similar incidence of autonomic dysfunction (P=0.899). We have excluded cardioembolic strokes due to possibility of their interference with autonomic function.

Table : Stoke subtype and Autonomic dysfunction			Holter autonomic dysfunction		
			NO	YES	Total
STROKESUBTYPE	LAA	Count	23	7	30
		% within Holter_AUTO_DYS	29.1%	31.8%	29.7%
	Lacunar	Count	27	6	33
		% within Holter_AUTO_DYS	34.2%	27.3%	32.7%
	Carotid dissection	Count	2	0	1
		% within Holter_AUTO_DYS	2.6%	0.0%	2.0%
	Undetermined	Count	27	9	36
		% within Holter_AUTO_DYS	34.2%	40.9%	35.6%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.899

Autonomic dysfunction and vascular complications: At the time of discharge, 10 out of 101 patients had acute vascular complications, of which 6 had a new coronary event and 4 had a recurrent stroke. There was no significant difference in incidence of vascular complications in patients with or without clinical autonomic dysfunction (P= 0.639 for clinical autonomic dysfunction). However, there was higher incidence of vascular complications in patients who had autonomic dysfunction on holter testing (P=0.006 for holter autonomic dysfunction).

Table : Clinical Autonomic dysfunction and Vascular complications			Clinical autonomic dysfunction		
			No	YES	Total
VASCULARCOMPLICATIONS	None	Count	54	18	72
		% within Clinical_AUTO_DYS	93.1%	90.0%	92.3%
	Coronary Events	Count	3	1	4
		% within Clinical_AUTO_DYS	5.2%	5.0%	5.1%
	New Stroke	Count	1	1	2
		% within Clinical_AUTO_DYS	1.7%	5.0%	2.6%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P=0.639

Table : Holter Autonomic dysfunction and Vascular complications			Holter autonomic dysfunction		
			No	Yes	Total
VASCULARCOMPLICATIONS	None	Count	75	16	91
		% within Holter_AUTO_DYS	94.9%	72.7%	90.1%
	Coronary Event	Count	3	3	6
		% within Holter_AUTO_DYS	3.8%	13.6%	5.9%
	Stroke	Count	1	3	4
		% within Holter_AUTO_DYS	1.3%	13.6%	4.0%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.006

Autonomic dysfunction and Infarct expansion:

8 out of 101 patients had infarct expansion after the stroke onset. 6 out of these 8 patients had autonomic dysfunction on holter testing which was found to be statistically significant (P=0.001). This was not significant for patients with clinical autonomic dysfunction(P=0.598)

Table : Clinical Autonomic dysfunction and Infarct Expansion			Clinical autonomic dysfunction		
			No	YES	Total
INFARCT EXPANSION	No	Count	55	18	73
		% within Clinical_AUTO_DYS	94.8%	90.0%	93.6%
	YES	Count	3	2	5
		% within Clinical_AUTO_DYS	5.2%	10.0%	6.4%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P=0.598

Table : Holter Autonomic dysfunction and Infarct expansion			Holter autonomic dysfunction		
			NO	YES	Total
INFARCT EXPANSION	NO	Count	77	16	93
		% within Holter_AUTO_DYS	97.5%	72.7%	92.1%
	YES	Count	2	6	8
		% within Holter_AUTO_DYS	2.5%	27.3%	7.9%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.001

Autonomic dysfunction and outcome at discharge: At the time of discharge, patients without autonomic dysfunction had a better outcome with higher number of patients attaining mRS 3 or less compared to patients with autonomic dysfunction (P<0.001 for clinical autonomic dysfunction and P=0.004 for holter autonomic dysfunction).

Table: Autonomic dysfunction and outcome at discharge			Clinical autonomic dysfunction		
			NO	YES	Total
mRS at discharge	0-3	Count	47	6	53
		% within Clinical_AUTO_DYS	81.0%	30.0%	67.9%
	4-6	Count	11	14	25
		% within Clinical_AUTO_DYS	19.0%	70.0%	32.1%
Total		Count	58	20	78
		% within Clinical_AUTO_DYS	100.0%	100.0%	100.0%

P<0.001

Table: Holter Autonomic dysfunction and outcome at discharge			Holter autonomic dysfunction		
			NO	YES	Total
mRS at discharge	0-3	Count	49	6	55
		% within Holter_AUTO_DYS	62.0%	27.3%	54.5%
	4-6	Count	30	16	46
		% within Holter_AUTO_DYS	38.0%	72.7%	45.5%
Total		Count	79	22	101
		% within Holter_AUTO_DYS	100.0%	100.0%	100.0%

P=0.004

Autonomic dysfunction and outcome during short term follow up:

At 3 months follow up, 65 out of 78 patients who underwent clinical autonomic function testing had a good outcome with mRS of 3 or less. Patients who had autonomic dysfunction on clinical testing had poor outcome at 3 months with higher mRS at discharge (P=0.011).

MRS at 3months	Clinical autonomic dysfunction				Total	
	Present		Absent			
	N	%	N	%	N	%
0-3	13	65.0	52	89.7	65	83.3
4-6	7	35.0	6	10.3	13	16.7
Total	20	100.0	58	100.0	78	100.0

P=0.011

Table: Clinical autonomic dysfunction and Outcome at 3 months (mRS)

Patients who had autonomic dysfunction on holter testing also had poor outcome at 3 months with higher mRS compared to those without autonomic dysfunction (P<0.01)

MRS at 3months	Holter autonomic dysfunction				Total	
	Present		Absent			
	N	%	N	%	N	%
0-3	5	22.7	73	92.4	78	77.2
4-6	17	77.3	6	7.6	23	22.8
Total	22	100.0	79	100.0	101	100.0

P<0.01

Autonomic dysfunction and outcome at last follow up (6months- 1 year after stroke onset):

Majority of our patients were followed up at 6months to 1 year after stroke onset (88 out of 101 patients who underwent holter testing, 70 out of 78 patients who underwent clinical testing). At last follow up, those with autonomic dysfunction either on clinical or holter testing continued to have poor outcome with higher mRS scores compared to those without autonomic dysfunction (P=0.012 for autonomic dysfunction on clinical testing and P<0.01 for autonomic dysfunction on holter testing)

MRS at 1year	Clinical autonomic dysfunction				Total	
	Present		Absent			
	N	%	N	%	N	%
0-3	10	58.8	46	86.8	56	80.0
4-6	7	41.2	7	13.2	14	20.0
Total	17	100.0	53	100.0	70	100.0

P=0.012

Table: Clinical autonomic dysfunction and Outcome at last follow up (mRS)

MRS at 1year	Holter autonomic dysfunction				Total	
	Present		Absent			
	N	%	N	%	N	%
0-3	5	26.3	59	85.5	64	72.7
4-6	14	73.7	10	14.5	24	27.3
Total	19	100.0	69	100.0	88	100.0

P<0.01

Table: Holter autonomic dysfunction and Outcome at last follow up (mRS)

Discussion

The present study is a prospective cross sectional study to assess the prevalence and predictors of autonomic dysfunction in patients with first ever ischemic stroke among the patients attending the outpatient department, stroke clinic and admitted in stroke ICU of our institute. The study has looked in to the short-term neurological and cardiovascular outcome in patients with autonomic dysfunction which was measured clinically and through holter monitoring, after 7 days of stroke onset up to a period of 3months post-stroke. To our knowledge, this is the first study which used both clinical and holter testing to document autonomic dysfunction and its influence on stroke outcome.

Demographic characteristics of the population

In the present study, nearly three fourths of the subjects were males. Population based studies[55] have shown that male stroke incidence rate was 33% higher and stroke prevalence was 41% higher than the females.

Two thirds of our patients were above 60 years of age, in concordance with higher incidence of stroke with increasing age in general population.

Stroke Risk factors:

Systemic Hypertension was the most common risk factor in the study population, seen in 64.4% of patients. 39.6% of patients were current or reformed smokers. Diabetes was the third most common risk factor, seen in 30.7% of patients. 23.8% of patients

had history of coronary artery disease and 8.9% were previously found to have dyslipidemia prior to stroke.

We collected data on antihypertensive medication as they may have influence of autonomic function and can be a confounding factor. Calcium channel blockers were the most common antihypertensive medication, with 18.8% taking one of the calcium channel blockers. ACEI/ARB (11.9%) and beta blockers (9.9%) were the next most common antihypertensive medication used by the patients.

Location of Stroke, Severity and subtype:

Majority of patients (52.5%) had a stroke of moderate severity, with NIHSS score ranging from 5 to 14. Stroke was mild in 19.8% and severe stroke with NIHSS more than 15 was noted in 27.7% of patients.

We included only anterior circulation strokes as stroke in posterior circulation, involving brainstem, may directly affect several parameters of autonomic function. Amongst our study population of anterior circulation strokes, two-thirds of stroke involved the left side while the other one third involved the right side.

Subcortical territory was the most common location of infarct, with 46.5% of patients having only subcortical infarcts and 21.8 % having both cortical and subcortical involvement. 31.7% of patients had infarcts only involving the cerebral cortex.

As insular involvement was considered an important predictor of autonomic dysfunction, we studied the involvement of insula in our stroke patients. 23.8% of strokes involved insular region in either hemisphere.

The etiology of stroke in our population was classified according to TOAST criteria. However, we excluded cases of proven cardioembolic stroke, which might be a

confounding factor for the objective of our study. The etiology of stroke was lacunar stroke in 32.7% of patients, Large Artery Atherosclerosis in 29.7% patients and was undetermined in 35.6% of patients. Carotid artery dissection was etiology of stroke in 2 patients. Other rare causes like coagulopathy and genetic causes like CADASIL were not found in our study probably because we excluded patients with young stroke (below 40 years of age), which is the common age group for these rare causes.

At the time of discharge from hospital, 79.2% of patients remained same or improved compared to their modified Rankin score at stroke onset while 20.8% patients worsened from the time of stroke onset.

At the time of discharge, vascular complications were noted in 10 patients (9.9%), of which 5.9% were coronary events (NSTEMI/STEMI) while 4% had recurrence of stroke.

Prevalence of Autonomic dysfunction in stroke:

Clinical autonomic testing was done in 78 out of 101 patients using bedside autonomic testing battery, comprising sympathetic tests- Orthostatic BP measurement, sustained handgrip and parasympathetic tests- Deep breathing test, Valsava and 30:15 ratio. Autonomic dysfunction was classified accordingly to Ewing's classification of autonomic failure[(1)]. Based on Ewing's classification, Clinical autonomic testing was normal in 58 patients (57.4%), early autonomic failure was noted in 11 patients (10.9%), definite autonomic failure was noted in 6 patients (5.9%) while 3 patients had atypical autonomic dysfunction. Clinical autonomic dysfunction could not be done in 23 patients due to severe stroke, preventing ability to perform clinical tests like valsalva, sustained handgrip, deep breathing and orthostatic BP measurement.

Overall, of the 78 patients who could be tested clinically, 74.4% had normal autonomic function while 25.6% had some degree of autonomic dysfunction.

24 hour Holter monitoring was done for all patients to determine autonomic dysfunction through measurement of heart rate variability. Based on available normative data, autonomic function was classified as normal or abnormal according to various frequency domain and time domain measures of heart rate variability. Among the study population, 78.2% had normal autonomic function on holter monitoring whereas 21.8% had autonomic dysfunction.

Predictors of Autonomic dysfunction in Stroke

In our study, we looked at various demographic characteristics and several factors previously known to influence autonomic dysfunction and tried to elucidate the predictors of autonomic dysfunction. Baseline characteristics like age, presence of risk factors- hypertension, diabetes, smoking, coronary artery disease and dyslipidemia were comparable between the groups with and without autonomic dysfunction. Sanders et al[52] found higher incidence of autonomic activation in hypertensives than normotensives. Hypertension was not found to predict autonomic dysfunction in our study as there was no significant difference in autonomic dysfunction between hypertensives and normotensives in our study (P= 0.27). However, Sanders et al studied BP variability and did not study heart rate variability or outcome as we did in our study. Though women had higher incidence of autonomic dysfunction on clinical testing compared to men, this was not found to be significant in holter monitoring, which was done for all patients.

As antihypertensive medication like beta blockers may have influence of autonomic function and can be a confounding factor, we studied the influence of these

medications on autonomic dysfunction. Our study did not find significant incidence of autonomic dysfunction in patients taking beta blockers or other antihypertensives.

In our study, stroke severity was found to be significant predictor of autonomic dysfunction, with severe stroke (higher NIHSS) having higher incidence of autonomic dysfunction (P=0.006 for clinical autonomic dysfunction and P=0.001 for holter autonomic dysfunction). Similar results were obtained in study done by Hilz et al[11] who found higher incidence of autonomic dysfunction in patients with higher NIHSS scores.

We did not find any difference in autonomic dysfunction between right and left sided strokes (P= 0.93). Previous studies by Naver et al[5] found that reduced heart rate variability was seen in right sided strokes. On the contrary, NASCET group[8] found that left-sided, not right-sided, brain infarction is associated with increased risk of sudden death, suggesting a role for lateralization of autonomic function. Vista investigators [9] found that there was no difference in functional outcome between patients with right or left hemisphere stroke. Our results were consistent with findings of Vista investigators.

The stroke subtype according to TOAST classification also did not have any influence on autonomic dysfunction (P=0.89). Xiong et al[53] also studied the influence of stroke subtype on autonomic dysfunction and did not find any difference in incidence of autonomic dysfunction based on stroke subtype.

We found that cortical location of infarcts was associated with a higher incidence of autonomic dysfunction compared to subcortical infarcts (P=0.04 for holter autonomic dysfunction). This may be explained by involvement of cortical structures like insula which are known to influence autonomic function.

We also studied the effect of insular involvement on autonomic dysfunction. In our study insular involvement was significantly associated with autonomic dysfunction (P=0.001). Johannesen et al[32] and Oppenheimer et al[29] also had similar results in their previous studies. Cheung et al[7] reviewed the influence of insula on autonomic dysfunction, cerebrogenic cardiac death and also reviewed the clinical and experimental evidence for role of insula in autonomic dysfunction.

Autonomic dysfunction in Ischemic stroke and Influence on Stroke Outcome:

In our study, autonomic dysfunction was found to be associated with poor outcome at discharge, with more number of patients with autonomic dysfunction having mRS>3 at discharge (P<0.001) and also with poor outcome at 3months (P=0.011). Xiong et al[1] also published similar results using clinical autonomic testing and classified autonomic dysfunction according to Ewing's classification. This study found poor functional outcome in patients with autonomic dysfunction compared to patients without autonomic dysfunction. Bassi et al [54] also published similar results. Our results were in concordance with previously published results on influence of autonomic dysfunction on short term outcome.

At last follow up in our study (6months to 1 year from stroke onset), patients who had autonomic dysfunction in post stroke period still continued to have poor outcome with higher mRS at last follow up (P<0.001).

During follow up, there was higher incidence of vascular complications (coronary artery disease and stroke) in patients with autonomic dysfunction (P=0.006). However, since the total number of patients with vascular complications in very small (9.9%), it is not possible to come to any conclusion based on these findings.

Comparability of bedside autonomic function testing and holter testing for detection of autonomic dysfunction:

We also intended to find the accuracy and comparability of clinical autonomic testing to holter testing for heart rate variability. To the best of our knowledge, ours is the first study to compare the two methods for autonomic function testing. However, clinical autonomic testing could not be done in some patients with severe stroke due to physical disability. Nonetheless, we found that results on clinical autonomic testing were non inferior to holter testing (P=0.30) with specificity of 77% but a poor sensitivity of 38.5%. The low sensitivity could be attributed to the fact that patients with severe and moderately severe stroke could not undergo clinical autonomic testing. These findings need further validation as sample size is small in our study to come to any conclusion.

Conclusions

1) Autonomic dysfunction has a high prevalence of nearly 20% in anterior circulation strokes.
2) Autonomic dysfunction is not influenced by age, gender, hypertension, diabetes or side of stroke involvement.
3) Stroke severity, cortical involvement and insular location are predictors of autonomic dysfunction after stroke
4) Autonomic dysfunction is associated with poor short term outcome after first ever ischemic stroke.
5) Bedside autonomic function testing produces results non-inferior to holter monitoring but has limitations in severe stroke.

Limitations

1) Bedside autonomic testing could not be done in all patients as patients with severe stroke were unable to perform the tests.
2) As cardioembolic strokes were excluded, impact of stroke due to all etiological subtypes on autonomic dysfunction could not be compared.
3) Number of patients with autonomic dysfunction and number of patients with vascular complications is too small to make any conclusions.

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ANNEXURE

Proforma of Thesis

1.1. Name of the patient: ----------

1.2 Hospital No----------

1.3. Age ---------- years

1.4 Sex ---------- 1.Male 2.female

1.5. If outpatient or inpatient ---------- ---------If outpatient date seen in OPD----------

1.6. If inpatient, date of admission. ---------- Time ----------

1.7. Date of symptom onset---------- Time----------

1.8 Phone No 1:----------

1.9 Phone No2:----------

2. Risk factors (1=yes, 2=No)

2.1. Hypertension---------- Duration in years ----------

2.2. Diabetes milletus---------- Duration in years ----------

2.3. Current smoking---------- pack years ----------

2.3a Ex smoker……Stopped ----------years back

2.3. b. Drug addiction ----------

2.3. c. Alcoholism----------

2.4. Coronary artery disease-------- Duration in years ----------

2.5. Valvular heart disease--------- Duration in years ----------

2.5a. if yes, Specify ----------

2.5. b. Prosthetic valve ----------

2.5. c. Sick sinus syndrome ----------

2.6. Congestive heart failure ---------- Duration in years ----------

2.7. Peripheral vascular disease--------

2.8. Hyperlipidaemia---------- Duration in years----------

2.9. Atrial fibrillation---------- Duration in years----------

2.9.1. If patient on pacemaker ----------

2.1.1. History of prior stroke ----------2.1.1.a. Date of ictus----------

2.1.2. History of prior TIA---------- 2.1.2.b. Date of ictus----------

2.1.3. History of migraine ----------

2.1.4. Known carotid disease----------

2.1.5. On medications:

a) Beta blockers _____

b) Calcium channel blockers _____

c) ACEI/ ARB _____

3.Symptoms (1=yes, 2=No)

3.1. Visual disturbances ----------1.Amaurosis fugax 3.Hemianopia 4.Diplopia 5. Blurring of vision 6. None

3.2. Weakness ---------- 1. face alone 2.arm 3.leg 4.arm and leg 5. Face arm and leg 6.None

3.3. Numbness/paresthesia ----------

3.4. Speech disturbances ----------1.Aphasia 2.Dysarthria3. Both 4.None

3.5. Vertigo----------

3.6. Ataxia----------

3.7. Confusion---------- 3.7.a. Loss of consciousness ----------

3.8. Headache ----------

3.9. Seizures ----------

3.9.1 Duration of symptoms if TIA ---------- minutes

3.9.2 Number of TIAs before admission----------

3.9.3. Symptoms if present on arrival (in patients with TIA) ----------

3.10. Symptoms of autonomic dysfunction prior to stroke onset:

a) Postural hypotension_____

b) Impaired sweating_____

c) Bowel/ bladder disturbance_____ If yes, specify_____

d) Erectile dysfunction_____

4. Clinical Examination (1=yes, 2=No)

4.1. Pulse rate---------- (If Regular =1, Atrial fibrillation =2)

4.2. Blood pressure at ER Systolic---------- diastolic --------- (first documented BP)

4.3. Bruit ----------

4.4. Weakness ----------

4.5. Numbness----------

4.6. Cerebellar signs----------

4.7. Aphasia----------

4.8. Dysarthria ----------

4.9. Hemianopia----------

4.9.2. Final impression----------

1. Right hemispheric 2.Left hemispheric 3.Posterior circulation4.undetermined

4.9.3 NIHSS at admission ----------

4.9.4. NIHSS at 24hours (if admitted on day of stroke or TIA onset) ----------

4.9.5. GCS on admission ----------

4.9.6. MRS prior to stroke ----------

4.9.7. ABCD score in patients with TIA----------

4.10. Signs of peripheral neuropathy_____

4.11. Autonomic testing:

a) **Parasympathetic** :
   1) Valsalva maneuver

   2) Deep breathing

   3) The 30:15 ratio

b) **Sympathetic**:
   1) Orthostasis

   2) Sustained handgrip

Ewing classification of autonomic failure:

1) Normal 2) Early 3) Definite 4) Severe 5) Atypical

5. Investigations

5.1. Blood glucose in ER----------

5.2. Serum cholesterol----------

5.3. LDL--------

5.4. HDL----------

5.5. Serum triglycerides.----------

5.6. ECG---------- 1.Normal 2.LVH 3.AF 4 Ischemic changes 4. Not done

5.7. Echo-trans thoracic ---------- 1.Normal 2.LV dysfunction 3.Mural thrombus 4. Valve disease 5.PFO 6.infective endocarditis 7.Not done.

5.7a.If valve disease, specify ----------

5.8. Transesophageal ---------- 1.Normal 2.LV dysfunction 3.Mural thrombus 4. Valve disease

5. PFO 6.inf endocarditis 7.Aortic plaques >4mm8.Not done

5.1.1. Vasculitic workup ----------1.Positive 2.Negative3.Not done.

5.1.1.a. If done, specify ----------

5.1.2. Prothrombotic work up ----------1.Positive 2.Negative3.Not done.

5.1.2.a. If done, specify ----------

6.Diagnostic imaging

6.1. CT scan ---------- 1.Normal.2. New infarct 3. Old infarct 4.Small vessel Ischaemic changes 5.Not done

6.1. A Territory ---------- 1. ICA 2.ACA 3.MCA-complete 4 MCA-Inf div 5 MCA sup div 6 MCA subcortical

7. Posterior circulation

6.2. CT angio ---------- 1.Normal 2.abnormal 3.not done

6.3. MRI scan ---------- 1. DWI negative 2.DWI positive single lesion3.DWI – Multiple lesions 4.Not done

6.3.1. Arterial territory of acute infarct---------- 1.ICA 2.ACA 3.MCA-complete 4. MCA-Inf div 5. MCA sup div 6. MCA subcortical 7. Posterior circulation

6.3.1. a. Describe the MRI findings (acute and old lesions) ----------

6.4. MRA ----------1.normal 2.abnormal 3.Not done

6.4.1. If abnormal specify----------

6.5. Carotid Doppler----------1.normal 2.abnormal 3.Not done

6.5.1. If abnormal, specify ----------

6.6. DSA---------- 1.normal 2.abnormal 3.Not done

6.6.1. If abnormal specify ----------

6.7. Final impression on vessel status (symptomatic vessel) ---------- 1. <50% stenosis 2. Moderate stenosis (50-69%) 3.severe stenosis 4.arterial dissection 5.vessel occlusion 6.Normal

6.7.1. Vessel involved ---------- 1. extracranial ICA 2.intracranial ICA 3.MCAM14.MCA M2.5.ACA6.BA.7.VA.8.PCA9.SCA10.PICA -

6.7.2. Side of involvement of vessel ----------1.Right 2.Left 3.Bilateral

6.7Stroke subtype----------1.large artery atherosclerosis 2.Cardioembolic.3Other Specific causes.4.Undetermined 5.lacunar

6.7. a. If cardioembolic, mention cause ----------

6.7. b. If specific cause ----------1.Dissection 2. Prothrombotic 3. Vasculitis 4. MoyaMoya

6.8. Arterial territory ---------- 1.ACA 2.MCA 3.PCA 4.VA.5.BA.6.ICA7.SCA8.PICA

Holter Monitoring:

1.Maximal heart rate (HR)

Minimal heart rate (HR);

2. premature ventricular contractions (PVC);

3. ventricular couplets (VC);

4. nonsustained ventricular tachycardia

5. premature supraventricular contractions (PSVC);

6. SVT, including atrial tachycardia and atrial fibrillation

7.Time domain measures –

a) SDNN

b) rMSSD

8. Frequency domain measures-

a) HF

b) LF

c) HF/LF ratio

7. **Thrombolysis**

7.1. If thrombolysed----------1.Yes 2.No

7.2. If yes ----------1.intravenous 2intraarterial 3.Bridging

7.3. If SICH after tPA----------1.Yes2.No

8. Treatment at discharge (1=yes, 2= No)

8.1. Aspirin----------

8.2. Clopidogrel----------

8.3. Heparin ----------

8.4. Warfarin ----------

8.5. Statins ----------

8.6. Antihypertensives ----------

8.7. Carotid endarterectomy---------- Date of surgery----------

8.8. Carotid stenting----------Date of stenting----------

8.9. Hemicraniectomy done ----------Date of surgery----------

8.9. a. PFO closure----------1.Yes 2.No

8.9.b. Moya- Moya Revascularization----------Date of surgery----------

9. Outcome

9.1. Date of discharge----------

9.2. Final diagnosis ----------1.Definite TIA 2.Probable TIA 3 ischemic stroke

9.2. Outcome at discharge (only mention if new events) ----------
1.normal.2.ischaemic

Stroke 3. Haemorrhagic stroke 4. MI 5.CCF 6.Recurrent TIA 7. Death

9.3. Date of new ischemic event ----------

9.4. If stroke arterial territory ----------1. ICA 2.MCAM1 3.MCA M2.4.ACA 5.BA.6.VA.7.PCA8.SCA9.PICA

9.4.1 NIHSS at discharge----------

9.4.2 Modified Rankin Scale at discharge----------

9.4.3. If died, cause of death----------1.Vascular 2.Non vascular

9.4.4. Cause of death, specify----------

9.5. 3 month outcome date ----------

9.5.1. Outcome at 3 month ---------- 1.Normal 2.Ischaemic stroke3.Haemorrhagic Stroke 4. MI 5. CCF 6. Recurrent TIA 7. Death

9.6. Date of event----------

9.7. Modified Rankin scale at 3 months----------

9.8. NIHSS at 3 months----------

9.9. If died, cause of death----------1.Vascular 2.Non vascular.

9.9.1. Cause of death, specify ----------

9.10. Outcome at 1year_____ 1.Normal 2.Ischaemic stroke3.Haemorrhagic Stroke 4. MI 5. CCF 6. Recurrent TIA 7. Death

9.10.1 . If died, cause of death----------1.Vascular 2.Non vascular.

9.10.2. Cause of death, specify ----------