ASSESSMENT OF AUTONOMIC FUNCTION IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE

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CERTIFICATE

This is to certify that this dissertation entitled "**ASSESSMENT OF AUTONOMIC FUNCTION IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE"** is a bonafide work done by **Dr. S. PRASANNA KARTHIK,** Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai – 3 in partial fulfilment of the University Rules and Regulations for the award of M.D. Branch – I General Medicine, under our guidance and supervision, during the Academic period from May 2011 to November 2011.

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I, **Dr. S. PRASANNA KARTHIK** solemnly declare that the dissertation entitled "**ASSESSMENT OF AUTONOMIC FUNCTION IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE**" is done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 600003 during the period May 2011 to November 2011 under the guidance and supervision of **Prof. P. CHITRAMBALAM M.D.** to be submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of the requirements for the award of M.D. DEGREE (Branch - I GENERAL MEDICINE).

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CONTENTS

INTRODUCTION

INTRODUCTION

Cerebrovascular diseases, of late has emerged as one of the leading contributors to the morbidity and mortality of our nation's population. Although it has a specific age predilection, in that being common among the elderly, it does not spare the young too in whom the effects are more dramatic, as a hale and hearty individual becomes nothing but a vegetable in an instant. It manifests as an abrupt onset of focal neurological deficits as if the patient has been "struck by the hand of God".

The morbidity the cerebrovascular disease causes is equal in effect to its mortality, as the functional recovery of the patient cannot be guaranteed. In this modern era of medicine, an effective cure for this disease is still elusive. It becomes therefore mandatory on the part of the treating physicians to alleviate the suffering of the patient, as much as possible.

The causes of stroke are many since it depends on the interplay of multiple factors present in the patient. The patient may present with arterial or venous stroke, ischemic or haemorrhagic stroke, anterior circulation or posterior circulation stroke. Thus, the combination of the factors, leads to a varied etiological,

pathological and clinical presentation which in the end leave a trail of devastation in the patient's life.

The patient who presents with acute cerebrovascular disease is traditionally evaluated to determine the extent of the involvement of the higher mental functions, cranial nerves, motor system, sensory system, extrapyramidal system and cerebellar functions. Autonomic function testing is usually not given its due importance. This is because of the complex nature of the autonomic function tests and the relative technical difficulty faced in administering the test to the patients.

A certain level of cooperation from the patient and a degree of mobility of the patient is definitely required to carry out the autonomic functions. As this is not usually possible in these bed ridden patients, a newer method to assess the autonomic dysfunction becomes mandatory. This role is well fulfilled by the simple and non-invasive measurement of resting heart rate variability. The measurement of heart rate variability in the resting state has been well documented to correlate with the findings of other autonomic function tests and can be useful as a single test instead of a battery of tests in patients where it is not possible to carry out such investigations.

The problem of autonomic dysfunction in patients with acute cerebrovascular diseases is still not given adequate importance as the mechanisms behind such dysfunction are still unclear. Newer models of cerebrocardiac interactions and the role of the insular cortex in maintaining the sympathovagal balance on the heart are being evolved and animal studies have provided newer insights. However the clinical implications of autonomic dysfunction have been well studied and documented in patients who have survived. It has been found to correlate well the morbidity and mortality of such patients. The effect of autonomic dysfunction on mortality and morbidity of patients with acute myocardial infarction and heart failure have been well established and the benefits of beta blockers have improved outcomes in these patients.

So the presence of autonomic dysfunction may play a role in the development of cardiac arrhythmias in patients with stroke and interventions directed towards reducing the incidence of it may play a role albeit in decreasing the morbidity as well as mortality associated with cerebrovascular diseases.

AIMS AND OBJECTIVES

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AIM

The present study was carried out to assess the status of the autonomic function in patients with a clinical diagnosis of acute cerebrovascular disease in a tertiary care setting and determine its influence on the morbidity and mortality.

OBJECTIVES

Primary Objective

To assess the status of autonomic function of patients when admitted to the Rajiv Gandhi Government General hospital, Chennai, a tertiary care referral hospital in the public sector which caters to the needs of the population of Tamilnadu as well as those from neighboring stateswith a clinical diagnosis of acute cerebrovascular disease.

Secondary Objectives

a) To assess the predictive value of autonomic dysfunction (if any) on the morbidity and mortality of patients with a clinical diagnosis of acute cerebrovascular disease

b) To identify potential areas of interventions that can improve the long term outcome in patients with a clinical diagnosis of acute cerebrovascular disease

REVIEW OF LITERATURE

REVIEW OF LITERATURE

DEFINITION

A stroke, or cerebrovascular accident, had been defined as the abrupt onset of a neurological deficit that is attributable to a focal vascular cause[1]. Thus, the definition of stroke is clinical, and the laboratory studies, including imaging studies, are used to support the diagnosis and not to make it.

WHO had defined stroke as a “rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin”.

The disturbance of the cerebral function could be caused by either of three major morphological abnormalities, i.e. stenosis, occlusion or rupture of the arteries or a combination of these three morphological abnormalities. Its manifestation therefore depends on the extent and site of the area involved as well as the underlying causes and might take the form of coma, hemiplegia, paraplegia, monoplegia, speech disturbances, cranial nerve paresis, sensory impairment, vertigo, or gait disturbances.

EPIDEMIOLOGY

Cerebrovascular disease has emerged as the third most common cause of death worldwide, after coronary heart disease and cancer[2]. Although the exact prevalence of cerebrovascular disease has not yet been estimated in India, the age standardized mortality rate for non-communicable diseases in India for the year 2008 had been estimated as 685 per 100,000 population[2].

The first epidemiological survey on stroke carried out by Abraham and co-workers in Vellore, Tamilnadu, indicated that the prevalence of stroke to be 52 per 100,000 population (in which cohort)[3]. However, studies carried out later in various regions of the country estimated the prevalence to range from 44 to 220 per 100,000 population[4, 5, 6, 7].

It had been estimated that stroke contributes to 1.2 % of the total deaths in India, when all ages were included. The proportion of stroke death increased with age, and in the oldest group (> 70 years of age) stroke contributed to as high as 2.4% of all deaths[8].

In 2005, estimates indicated that 58 million people died worldwide, and in them chronic diseases accounted for 35 million deaths (60%). Cardiovascular diseases, predominantly heart disease and stroke, were the cause of death in 17.5 million

individuals. After heart disease, stroke is the second leading single cause of death, with 5.8 million fatal cases per year, 40% of which are in people younger than 70 years[9].

Asians have a lower rate of coronary heart disease and a higher prevalence of stroke. Among the Asians, the number who died from stroke was more than three times that for coronary heart disease. The disparity between the incidence rates for stroke and coronary heart disease had been attributed to high prevalence of hypertension and low levels of blood lipids among the Orientals[10]. Hypertension was related to high salt intake and perhaps to genetic factors and low serum lipid was due to low levels of animal fats and protein in the oriental diet. However, detailed epidemiological data and the annual incidence rate of stroke in India is still lacking due to the absence of a strong surveillance system in India.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is that part of the peripheral nervous system that acts as a control system functioning largely below the level of consciousness, and controls visceral functions. It is classically divided into two subsystems: the parasympathetic nervous system and the sympathetic nervous system. The sympathetic division has thoracolumbar “outflow”,

meaning that the neurons begin at the thoracic and lumbar (T1-L2) segments of the spinal cord. The parasympathetic division has craniosacral “outflow”, meaning that the neurons begin at the cranial nerves (CN 3, CN7, CN 9, and CN10) and sacral (S2-S4) segments of the spinal cord.

CEREBROCARDIAC INTERACTION

The concept of central integration in cardiac and vascular regulation can be better understood by knowing that any increase in blood pressure and cardiac output increases the activity of the afferent pathway, which reflexively inhibits sympathetic activity or activates parasympathetic activity or both. However, any decrease in blood pressure and cardiac output decreases afferent activity, which reflexively increases excitatory responses. Thus, cardiovascular function is controlled by a negative-feedback system, and increasing activity of the afferent pathway results in decreasing activity of the sympathetic efferent pathway and/or increasing activity of the parasympathetic efferent pathway and vice versa[11].

In the afferent pathways, arterial baroreceptors located in the carotid sinus, aortic arch, and various thoracic arteries respond to changes in blood pressure and give rise to afferent activity, which conducts in the glossopharyngeal and vagus nerves. The

cardiac mechanoreceptors are sensitive to mechanical deformation of the cardiac chambers and gives rise to afferent activity, which conducts in the vagus nerve. The pulmonary stretch receptors are sensitive to lung volumes, and inhalation increases afferent activity, which conducts in the vagus nerve[11].

In the efferent pathways, the sympathetic nervous system (SNS) is predominantly involved in cardiac and vascular regulation, and the parasympathetic nervous system (PNS) only has a little influence on the peripheral vasculature. Postganglionic sympathetic fibers innervate the atria, the ventricles, and coronary arteries from the cervical ganglia as the superior, middle, and inferior cardiac nerves or from thoracic ganglia at the T1-T4 level. Stimulation causes increased heart rate, increased myocardial contractility, and coronary vasodilatation[11].

Postganglionic sympathetic fibers innervate the vasculature from plexus on the large proximal vessels or from the somatic nerve. The innervation is denser in resistance vessels (small arteries and large arterioles) than in capacitance vessels (venules and veins). A balance of alpha adrenergic (vasoconstricting) and beta adrenergic (vasodilating) innervation exists. Preganglionic parasympathetic fibres innervate the atria, the ventricles, and coronary arteries from the vagus either by the

superior and middle cardiac rami or by the recurrent laryngeal nerve as the inferior cardiac rami. Stimulation causes decreased heart rate, coronary vasoconstriction and decreased contractility[11].

The central autonomic network is a complex network in the central nervous system that integrates and regulates autonomic function. The network involves the cerebral cortex (the insular and medial prefrontal regions), amygdala, striaterminalis, hypothalamus, and brainstem centers (periaqueductal gray, parabrachial pons, nucleus of the tractussolitarius, and intermediate reticular zone of the medulla)[11].

It has been well established that hemispheric lesions altering the wide spread central autonomic network may impair the baroreflex function[12]. Baroreflex dysfunction had been said to play a role in hypertension, coronary artery disease, myocardial infarction, and chronic heart failure. Baroreflex impairment in conjunction with reduced vagal inhibitory outflow results in chronic activation of the sympathetic nervous system. A sustained increase in sympathetic activity contributes to end-organ damage and to disease progression and may predispose to subsequent cardiovascular events. It is clinically important to note that impaired cardiac baroreceptor reflex sensitivity has been shown to independently predict mortality and the incidence of adverse

cardiovascular events in hypertension or after myocardial infarction and had been associated with a poor prognosis in chronic heart failure[13, 14].

Disease manifestations that indicate baroreceptor reflex dysfunction, such as hypertensive crises or high blood pressure variability, often accompany the acute phase of ischemic or haemorrhagic stroke[15]. It had been shown consistently that the impairment of baroreflex is present in patients with acute ischemic and haemorrhagic stroke[12, 15, 16, 17]. The level of baroreflex dysfunction did not differ between ischemic stroke and intracerebral haemorrhage, albeit different mechanisms could be anticipated[18]. Underlying pathophysiologic mechanisms are generally unknown; however, there is increasing evidence that the central autonomic network is involved. The insular cortex plays a principal role in modulating baroreflex sensitivity[19, 20, 21]. The baroreflex sensitivity was found to be impaired in stroke patients with left and/or right insular involvement compared with patients without insular involvement or control subjects[17]. This finding suggests that both insulae may participate in the regulation of baroreflex. Both the left and right insulae have been previously suggested to modulate baroreflex sensitivity[19, 20, 21, 22]. The baroreflex-related neuronal interconnections have been observed

between the right and left insulae, suggesting that both the insulae probably interact in integrating circulatory control information[23].

Controversy exists on the topic of proposed hemispheric lateralization of the baroreflex and/or autonomic control. Sykora and co-workers showed that lesions involving the area of left insula decreased baroreflex sensitivity significantly more than lesions of right insula[24]. Similar findings were demonstrated by Hilz et al, who showed a decrease in baroreflex sensitivity in conjunction with left-sided hemispheric inactivation in epilepsy patients[25]. Studies carried out by Zamirini et al and Oppenheimer et al showed right-sided dominance of sympathetic and left-sided dominance of parasympathetic modulation[26,27].

On the other hand, studies carried out by Naver et al and Meyer et al indicated that in patients with ischemic stroke, there is a reduction in parasympathetic and an increase in sympathetic heart rate modulation with right sided strokes[28,29]. At this point of time, it is not clear whether the right or left insula control central autonomic function.

The investigation of baroreflex changes in patients with acute cerebrovascular diseases represents a technical and methodological challenge. This is because the disease is frequently associated with carotid atherosclerosis, heart failure,

coronary artery disease, a history of hypertension, and previous antihypertensive treatment. These conditions are well known to alter the baroreflex function and hence revealing the true aetiology of stroke related baroreflex changes is complex[30]. In the study by Sykora et al, the impairment of baroreflex was seen in patients with acute cerebrovascular diseases and this was seen to be independent of carotid artery atherosclerosis. They also observed that there was decreased baroreflex function in stroke patients compared with controls matched for atherosclerosis and other possible confounding factors, which were attributed to lesions affecting central autonomic regions[31].

Factors like age, heart failure, coronary artery disease, diabetes mellitus, history of hypertension and previous antihypertensive treatment represent confounders for the assessment of baroreflex sensitivity in acute stroke. Hence, earlier studies examining baroreflex sensitivity in acute stroke excluded patients with heart failure, coronary artery disease, and a history of myocardial infarction or diabetes to prevent bias. However, Sykora et al found no statistical significant influence when tested for this. The effects of age and hypertension on baroreflex sensitivity, albeit not significant, were seen in the control group. They hypothesized that these effects were also present in the stroke

group but were presumably outweighed by stroke-related changes in baroreflex sensitivity[31].

Patients presenting with a shift in autonomic balance were found to be at increased risk for developing cardiac complications and demonstrated a significantly higher cardiovascular morbidity and mortality[32, 33, 34].The possible pathophysiologic mechanisms which can be associated with this high risk include raised arrhythmogenic potential, increased platelet aggregability, coronary vasoconstriction and impaired ventricular remodelling, which are all known to be associated with increased sympathetic activity.

Laowattana et al found that left insular stroke was associated with a significantly adverse long term cardiac outcome, particularly in patients without coronary artery disease[35]. They proposed that there is involvement of the baroreflex arch with decreased parasympathetic tone and increased sympathetic drive in these patients which were responsible for the adverse outcomes. Other manifestations of autonomic dysfunction after insular stroke include disturbed circadian blood pressure patterns, higher norepinephrine levels, cardiac arrhythmias or QT prolongation which can explain the various interplaying

mechanisms that contribute to the adverse outcome in these patients[36, 37].

CLINICAL IMPLICATIONS

Acute cerebrovascular disease is associated with an adverse long term cardiac outlook which is possibly relating to altered sympathovagal balance[38]. Barron et al have reported that when compared with age/gender matched controls, the total spectral power of RR intervals was reduced after an episode of acute cerebrovascular disease. The power associated with cardiac parasympathetic neural activity was particularly affected indicating a shift in the sympathovagal balance[39]. Strittmatter et al and Giubilei et al also reported elevation of the sympathetic cardiac tone in the acute phase of stroke and this was found to persist upto three weeks[40,41].

Sander et al have reported that the absence of circadian cardiovascular variation was particularly striking after insular infarction. In these patients, the plasma noradrenaline levels were higher. Also an elevated nocturnal blood pressure, a higher incidence of QTc interval prolongation and ventricular arrhythmias was demonstrable when compared to patients with stroke in other locations[42, 43,44].

Wolf et al first reported on the association between reduced heart rate variability and higher post infarction mortality, sudden cardiac death, and arrhythmias in patients recovering from acute myocardial infarction[45]. In neurologic conditions, heart rate variability has been studied in patients with diabetic neuropathy, spinal cord injury and brain death[46, 47, 48, 49, 50]. A study of heart rate variability in children with head trauma showed a significant decrease in the low frequency / high frequency (LF/HF) ratio among patients with high intracranial pressure and reduced cerebral perfusion pressure and those who progressed to brain death[51]. In a study of 29 neurosurgical patients treated in an intensive care unit, poor recovery and death were associated with reduction of total power of HRV, power in VLF and LF bands, and decreased LF/HF ratio[52].

Few studies have addressed heart rate variability in the context of acute stroke. Kawecka et al reported a decrease in the heart rate variability among 36 patients with acute stroke (ischemic and haemorrhagic) and hypertension, compared with age-matched control subjects with hypertension[53]. Meglic et al evaluated heart rate variability in 14 patients with acute brainstem strokes and compared the profiles in medullary and non-medullary strokes. The integrals over HF and LF spectral bands were significantly

smaller in patients with medullary strokes, whereas those with non-medullary strokes had HRV profiles similar to controls, suggesting the occurrence of autonomic dysfunction in medullary stroke[54]. Tokgozoglu et al studied the heart rate variability profiles of 62 patients with ischemic stroke and 62 controls. All patients with stroke had significantly decreased power in LF and HF bands. However, patients with right-middle cerebral artery and insular infarcts had significantly lower power compared with all other localizations suggesting a possible selective influence of these regions of the brain over cardiac autonomic function[55].

Sykora et al hypothesized that autonomic dysfunction in acute stroke as expressed by decreased baroreflex sensitivity may have effects on outcome in the following ways:

a) Inadequate cerebral perfusion due to the increased blood pressure variability and impaired cerebral auto regulation
b) Increased cardiovascular complications
c) Secondary brain injury due to inflammation, hyperglycemia, and blood– brain barrier disruption[24].

The knowledge about baroreflex dysfunction in acute cerebrovascular diseases raised questions regarding the therapeutic implications of this finding. Baroreflex sensitivity can

be positively influenced by certain drugs, especially beta blockers[56,57]. Loawattana et al showed that among 111 ischemic stroke patients, the use of beta blockers was independently associated with less severe stroke on presentation and that sympatholytic effects may have cerebroprotective properties[58]. In an animal model, beta blockers given before the induction of experimental ischemia led to a reduction in infarct volume by 40%[59]. In an analogous way, beta blockers reduced brain edema in a histological model of traumatic brain injury[60]. Positive effects of beta blockade on outcome have also been reported in patients with traumatic brain injury[61, 62].

The use of beta blockers in acute human stroke may appear controversial. Atenolol and propranolol tested in a randomized, controlled study of 302 acute stroke patients showed a trend toward increased death and disability in the treatment group[63]. Through negative inotrope activity, beta blockers may potentially reduce global cerebral blood flow. However, other studies did not demonstrate any harmful effect of beta blockers in acute stroke; on the contrary, possible neuroprotective properties have been advocated[64, 65, 66]. Clonidine, moxonidine, and mecobalamin may also improve baroreflex sensitivity. A central mechanism of action is supposed in the effects of clonidine and

moxonidine, whereas a peripheral mechanism is suggested for mecobalamin[67, 68]. Clonidine was also shown to increase the activity of baroreceptive neurons in the ventrolateral medulla, enhance the slope of the cardiac baroreflex, and reduce pressure lability[69].

New devices stimulating baroreceptors are emerging in the treatment of chronic refractory hypertension. Mediated through the central sympathoinhibitory effect by stimulating the carotid baroreceptors electrically, these devices ameliorate baroreflex sensitivity and reduce hypertension. On-going trials on these devices are finding significant and sustained reductions in blood pressure, a good safety profile, and tolerable side effects[70]. However, the evidence is insufficient to draw further conclusions, in particular regarding acute stroke therapy.

AUTONOMIC FUNCTION TESTING

With the evolution and validation of reliable non-invasive techniques, the evaluation of autonomic disorders is more widely available. Numerous techniques to evaluate autonomic functions had been described, of which cardiovagal, adrenergic and sudomotor functions are most common methods involved. This study is done by testing the cardiac autonomic functions. Though the pathogenesis of cerebrovascular diseases involves the central

nervous system, appropriateness of studying the cardiac autonomic regulation as a replacement for examining the cerebral autonomic regulation is supported by several studies.

Zvan et al while examining the effects of activation of sympathetic nervous system in rats found an increase in heart rate and mean blood velocity in the middle cerebral artery suggesting that autonomic dysregulation that affected cardiac function also affected the cerebral vascular activity[71]. Therefore it appears appropriate that the study of cardiac autonomic nervous system will be closely associated with cephalic vasomotor response.

For diagnostic purpose it is preferable to perform a battery of tests rather than to rely on single test to determine the intactness of autonomic reflex[72]. The most commonly used test of autonomic function relies on heart rate and blood pressure changes in response to breathing, and to posture changes. These tests are simple, non-invasive, easy to perform & reproduce, and are both sensitive as well as specific[73].

The following tests are usually carried out to assess the Autonomic Nervous System functioning namely Heart rate response to deep breathing, Heart rate response to Valsalva manoeuvre, Heart rate response to standing (30:15 ratio), Beat to beat BP response to Valsalva manoeuvre during phase IV, Heart

rate and BP response to active standing, Diastolic BP and heart rate response during cold pressor test, BP and heart rate response during and after 5 minutes of isometric hand grip test. However these are not feasible in a patient afflicted with stroke because of his debilitation or because of technical restrictions. Hence it becomes paramount to ascertain a more suitable and non-invasive method of assessment of autonomic function in these patients

Sztajzel et al have stated that among the different available non-invasive techniques for the assessment of autonomic status, heart rate variability has emerged as a simple non-invasive method to evaluate sympathovagal balance at the sino-atrial node[74].

HEART RATE VARIABILITY

The intrinsic firing rate of uninnervated human sinoatrial node (SA) is 100 beats per minute. In an innervated heart the sympathetic system will increase the rate of depolarization of sinoatrial node, while parasympathetic innervation supplied by vagus nerve decreases the firing rate of sinoatrial node. The net accelerating and decelerating influences of the cardiac sympathetic and parasympathetic system will determine the cardiac sympathetic tone and cardiac parasympathetic tone. The predominance of resting vagal tone over sympathetic tone is

responsible for heart rate below 100. The heart rate is conventionally measured by noting the number of heart beats per minute. The duration of cardiac cycle of all heart beats occurring in one minute, even under resting condition is not the same. There is beat to beat variability of RR interval in milliseconds. This spontaneous beat to beat variation is known as HEART RATE VARIABILITY (HRV).

Donald Moss & Fred Shaffer aptly described that “The human heart is a bioelectrical pump, beating at ever changing rate: it is not like a clock that beats at a steady unchanging rate”. The sympathetic activity will decrease the RR interval and parasympathetic will increase the RR interval. So heart rate variability can be used as one of the non-invasive tests to evaluate the integrity and functional state of Autonomic Nervous System.

The assessment of Heart rate variability has undergone a remarkable sea of change from the early days when it was first demonstrated by Hon and Lee in the year 1965[75]. With the availability of new, digital, high frequency, 24-h multi-channel electrocardiographic recorders, the significance and meaning of the many different measures of Heart Rate Variability became more complex. There arose a potential for incorrect conclusions and for excessive or unfounded extrapolations. The recognition of

these problems led the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to constitute a Task Force charged with the responsibility of developing appropriate standards. The task force came out in 1996 with the “Heart rate variability Standards of measurement, physiological interpretation, and clinical use Guidelines[76]”.

The heart rate variability can be assessed with the use of time domain methods or frequency domain methods as per the guidelines.

TIME DOMAIN METHODS

The time domain methods measure either the heart rate at any point in time or the intervals between successive normal complexes. From these measurements 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 and the difference between night and day heart rate. From a series of instantaneous heart rates or cycle intervals, particularly those recorded over longer periods, traditionally 24 h, more complex statistical and geometric time-domain measures can be calculated.

The statistical time domain measures may be divided into two classes, (a) those derived from direct measurements of the

NN intervals or instantaneous heart rate, and (b) those derived from the differences between NN intervals. They include:

a) SDNN – Standard deviation of all NN intervals (measured in ms).
b) SDANN – Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording (measured in ms).
c) RMSSD – The square root of the mean of the sum of the squares of differences between adjacent NN intervals (measured in ms).
d) SDNN index – Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording (measured in ms).
e) SDSD – Standard deviation of differences between adjacent NN intervals (measured in msec).
f) NN50 count – Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. Three variants are possible counting all such NN intervals pairs or only pairs in which the first or the second interval is longer.
g) pNN50% – It is the NN50 count divided by the total number of all NN intervals.

In general, the statistical time domain methods are more likely to deliver a better assessment of the autonomic function when assessed over a longer period of 24 hours rather than short term recordings of 5 minutes.

The geometrical time domain measures are derived by converting the series of NN intervals into a geometric pattern and analysing them. They include:

a) HRV triangular index – Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on discrete scale with bins of 7·8125 ms (1/128 s).
b) TINN – Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals (measured in ms).
c) Differential index – Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights (e.g. at the levels of 1000 and 10 000 samples) (measured in ms)
d) Logarithmic index Coefficient φ of the negative exponential curve $k \cdot e^{-\varphi t}$ which is the best approximation of the histogram of absolute differences between adjacent NN intervals.

The major advantage of geometric methods lies in their relative insensitivity to the analytical quality of the series of NN

intervals. The major disadvantage is the need for a reasonable number of NN intervals to construct the geometric pattern. In practice, recordings of at least 20 min (but preferably 24 h) should be used to ensure the correct performance of the geometric methods, i.e. the current geometric methods are inappropriate to assess short-term changes in HRV[76].

FREQUENCY DOMAIN METHODS

Various spectral methods for the analysis of the tachogram have been applied since the late 1960s. Power Spectral Density analysis provides the basic information of how power (i.e. variance) distributes as a function of frequency.

Methods for the calculation of Power Spectral Density may be generally classified as non-parametric and parametric. In most instances, both methods provide comparable results. The advantages of the non-parametric methods are: (a) the simplicity of the algorithm employed (Fast Fourier Transform – FFT) and (b) the high processing speed, whilst the advantages of parametric methods are: (a) smoother spectral components which can be distinguished independently of preselected frequency bands, (b) easy post-processing of the spectrum with an automatic calculation of low and high frequency power components and easy identification of the central frequency of each component, and (c)

an accurate estimation of PSD even on a small number of samples on which the signal is supposed to maintain stationarity. The basic disadvantage of parametric methods is the need to verify the suitability of the chosen model and its complexity.

Among short term recordings of 5 minutes duration, three main spectral components are distinguished.

- Very low frequency (VLF) [Range ≤ 0.04Hz]
- Low frequency (LF) [Range 0.04 – 0.15 Hz] and
- High frequency (HF) [Range 0.15 – 0.40 Hz]

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. The physiological explanation of the VLF component is much less defined and the existence of a specific physiological process attributable to these heart period changes might even be questioned. The non-harmonic component which does not have coherent properties and which is affected by algorithms of baseline or trend removal is commonly accepted as a major constituent of VLF. Thus VLF assessed from short-term recordings of 5 min is a dubious measure and should be avoided when interpreting the Power Spectral Density of short-term recordings.

Measurement of VLF, LF and HF power components is usually made in absolute values of power (ms^2), but LF and HF may also be measured in normalized units (n.u.) which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in n.u. emphasizes the controlled and balanced behaviour of the two branches of the autonomic nervous system. Moreover, normalization tends to minimize the effect on the values of LF and HF components of the changes in total power[76].

REQUIREMENTS FOR RECORDING

a) *ECG SIGNAL*

The fiducial point recognised on the ECG tracing which identifies a QRS complex may be based on the maximum or baricentrum of the complex, on the determination of the maximum of an interpolating curve, or found by matching with a template or other event markers. A limited sampling rate induces an error in the HRV spectrum which increases with frequency, thus affecting more high frequency components. Hence a higher sampling rate is preferable.

b) *DURATION OF ECG RECORDING*

Frequency–domain methods should be preferred to the time–domain methods when investigating short term recordings.

The recording should last for at least 10 times the wavelength of the lower frequency bound of the investigated component, and, in order to ensure the stability of the signal, should not be substantially extended. Thus, recording of approximately 1 min is needed to assess the HF components of heart rate variability while approximately 2 min are needed to address the LF component. In order to standardize different studies investigating short-term HRV, 5 min recordings of a stationary system are preferred unless the nature of the study dictates another design. Although the time–domain methods, especially the SDNN and RMSSD methods, can be used to investigate recordings of short durations, the frequency methods are usually able to provide more easily interpretable results in terms of physiological regulations. In general, the time–domain methods are ideal for the analysis of long-term recordings

c) *EDITING OF THE RR INTERVAL SEQUENCE*

The errors imposed by the imprecision of the NN interval sequence are known to affect substantially the results of statistical time domain and all frequency domain methods. It is known that casual editing of the RR interval data is sufficient for the approximate assessment of total HRV by the geometric methods, but it is not known how precise the editing should be to ensure correct results from other methods. Thus when using the statistical

time domain and/or frequency domain methods, the manual editing of the RR data should be performed to a very high standard ensuring correct identification and classification of every QRS complex. Automatic 'filters' which exclude some intervals from the original RR sequence (e.g. those differing by more than 20% from the previous interval) should not replace manual editing as they are known to behave unsatisfactorily and to have undesirable effects leading potentially to errors[76].

INTERPRETATION OF COMPONENTS

Vagal activity is the major contributor to the HF component. Disagreement exists in respect of the LF component. Some studies suggest that LF, when expressed in normalized units, is a quantitative marker for sympathetic modulations, other studies view LF as reflecting both sympathetic and vagal activity. Consequently, the LF/HF ratio is considered by some investigators to mirror sympathovagal balance or to reflect sympathetic modulations. Physiological interpretation of lower frequency components of HRV (that is of the VLF and ULF components) warrants further elucidation.

It is important to note that heart rate variability measures fluctuations in autonomic inputs to the heart rather than the mean level of autonomic inputs. Thus both autonomic withdrawal and a

very high level of sympathetic input lead to diminished heart rate variability[76].

PATIENTS & METHODS

PATIENTS AND METHODS

The present study was a prospective, controlled, open-label study carried out between May and November 2011 on patients who were admitted to the Rajiv Gandhi Government General hospital, Chennai, a tertiary care referral hospital which caters to the needs of the population of Tamilnadu and those from neighbouring states such as Andhra Pradesh and Karnataka with a clinical diagnosis of acute cerebrovascular disease. The protocol of the study was approved by the Institutional Ethics Committee, Madras Medical College Chennai 600003 and detailed informed written consent was obtained prior to enrolment in the study either from the patient (if possible) or else from the legal guardian of the patient.

STUDY POPULATION

One hundred (100) patients admitted to the various medical wards of Rajiv Gandhi Government General Hospital, Chennai were enrolled for the present study.

INCLUSION CRITERIA

The following were the criteria for enrolment in the present study:

a) Age : Above 18 years

b) Sex : Either sex

c) In patient/Outpatient: In-patient

d) Clinical diagnosis : Acute Cerebrovascular Disease (defined as onset of the symptoms less than 7 days) as confirmed by clinical and/or radiological evidence of neurological deficit(s)

EXCLUSION CRITERIA

The following groups of patients were excluded from the study.

a) Patients with history of established cerebrovascular accident
b) Patients with established intra-cardiac conduction defects which could interfere with the interpretation of results
c) Patients with advanced hepatic, renal or cardiovascular diseases which precluded their enrolment in to the study due to the critical nature of their comorbid illnesses.
d) Pregnant or lactating women
e) Those who were unwilling to sign the informed written consent

After obtaining written informed consent, a single investigator interviewed and evaluated all the patients with necessary help from the nursing staff as required. Relevant demographic data

required for identification purposes, were sought. A semi structured questionnaire (**Appendix A**), which was prepared earlier was administered by the Principal Investigator of the study. All the relevant information obtained by the interview, examination, investigation and evaluation of the patient were filled in by the Principal Investigator of the study.

The blood pressure was recorded with a mercury Sphygmomanometer in the supine position in all patients after ensuring that they had remained in the same position for at least a minimum of five minutes. A total of three readings were obtained from the arm which was not involved and the lowest of the three was taken for entry in to the study.

The severity of the stroke was established using the NIHSS-National Institute of Health Stroke Scale (**Appendix B**).

RECORDING OF ELECTROCARDIOGRAM FOR ANALYSIS

ECG tracings were obtained using NIVIQURE Ambulatory Digital ECG Recorder (INCO). All patients who were conscious and ambulant were instructed to empty their bladders prior to the recording. In patients who were unconscious or not ambulant, a sterile catheterisation of the urinary bladder was performed in the usual way and connected to a urinary bag and urine was drained. All patients were allowed to rest in the supine position for five

minutes in a calm and isolated room in the wards. After five minutes, the electrodes were placed on the chest in the Right infraclavicular, Left infraclavicular, Right inguinal and Left inguinal regions. The electrodes were connected to the recording machine and through the machine to the computer for recording the electrocardiogram. The recorder was precalibrated to the following settings to ensure uniformity in the recordings. The sampling rate was set to 1024 Hz and the recording interval was set to 320 sec (5min = 300 sec with 10 sec lead in and 10 sec lead out period). The machine was turned on and the recording was done with the patient remaining in the same posture throughout the entire period of the study.

At the end of the time window, the electrodes were disconnected and the recording was transferred to the computer. The recorded data was screened for the presence of artefacts and appropriately edited according to guidelines to ensure the validity of the result. The edited data was opened through the Heart Rate Variability Analysis Software (version 1.1, Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) and analysed. Power spectral analysis of the data was done using the Fast Fourier Transformation algorithm and the power of the very low frequency (VLF), low frequency (LF) and

high frequency (HF) bands were noted down. The ratio of LF to HF (LF/HF) was calculated by the software and the value was also noted.

Relevant basic laboratory investigations including complete blood count, renal parameters andblood sugar were undertaken from a single sample of blood taken at the time of admission. The findings from a relevant radiological investigation either CT Brain Plain or MRI Brain with MRA / MRV were included in the study depending on the investigation done for the patient. A baseline Electrocardiogram was also done in the supine position to rule out the presence of any conduction abnormalities in the patient

The patient was followed up during their period of stay in the hospital and the outcome was noted as either survived or died at the end of their stay in the hospital.

STATISTICAL ANALYSIS

The data collected from the patients were entered in to the master chart prepared. The statistical analysis was done using Graphpad Prism version 5. For non-parametric data, Chi square test was used. For parametric data, student's t-test or ANOVA (ANalysis of One way VAriance) was done as deemed appropriate to the data of interest.

OBSERVATION & RESULTS

OBSERVATIONS

AGE/ SEX DISTRIBUTION

The study involved a total of 100 (hundred) patients. The demographic characteristics of the enrolled subjects are presented in **Table 1 and 2.** Of the whole study population, there were 57 males and 43 females with an age range of 26 to 93 years. The age group distribution (**Fig.1.**) indicated that the major brunt of the illness was felt by the patients in the age group 55 to 75 years. A majority of patients affected among the study population were male (**Fig.2**).

Table 1: Age group distribution

AGE GROUP	NO of PATIENTS
25-34	4
35-44	8
45-54	17
55-64	29
65-74	26
75-84	12
85+	4

Table 2: Sex distribution

SEX DISTRIBUTION	
Male	57
Female	43

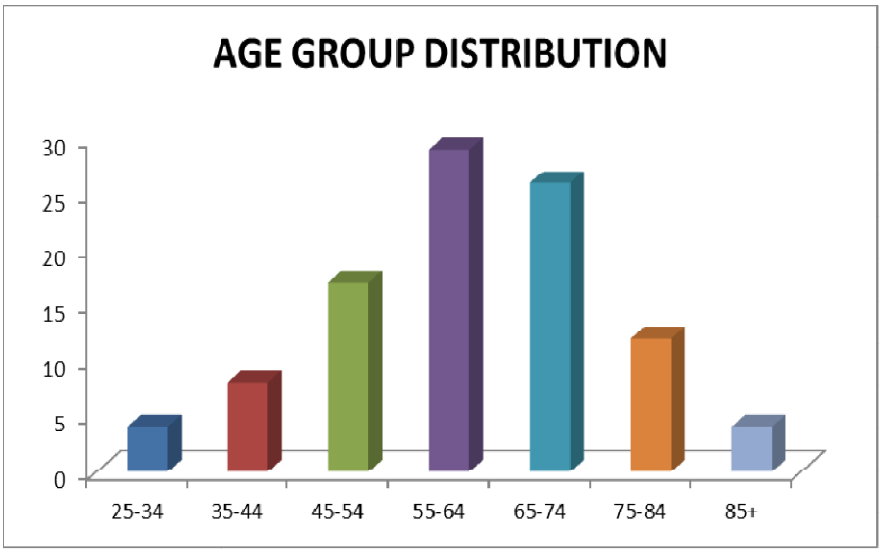

Figure 1: Age group distribution of the study population

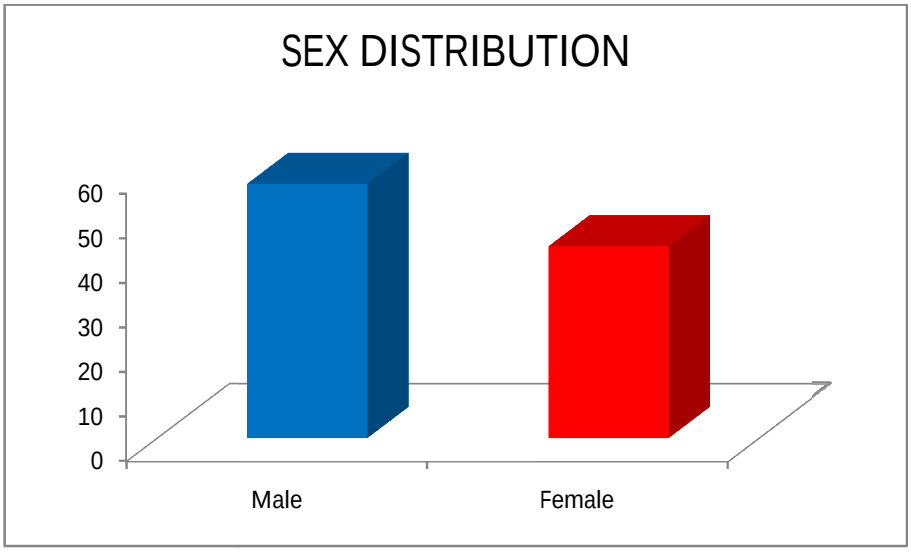

Figure 2: Sex distribution of the study population

Risk factors for stroke

Diabetes and Hypertension

Twenty seven (47.36%) of the male patients had a history of type 2 diabetes mellitus while among female patients it was only 39.53% (n=17). Similarly twenty six of the male patients had systemic hypertension while 45.6% of the female patients had systemic hypertension. Only 26.13 % of males (n=15) and 22.73% of females (n=10) did not have any of the above risk factors.

Table 3: Risk factor distribution

RISK FACTOR	MALE	FEMALE
Diabetes Mellitus (DM)	16	7
Systemic Hypertension (SHT)	15	16
DM + SHT	11	10
None	15	10

Smoking and alcoholism

Among the females, there was only one alcoholic and no smoker. Among the males, 52.36% (n=30) accepted that they were active smokers while an equal number were found to be having an active alcohol habit. 28.07% (n=14) of the males had a combined habit. Only 22.81% (n=13) of the males did not have any habit.

Table 4: Risk factor distribution

RISK FACTORS	Alcoholism	Smoking	Both	None
Males	14	14	16	13
Females	1	0	0	42

DETAILS OF STROKE

Day of presentation to the hospital

The day patients presented themselves to the hospital ranged from Day 1 to Day 7 after having been treated at various centres. Thirty six patients presented to the hospital within 48 hours of onset of symptoms whereas a nearly equal number, 37 of them, presented to the hospital more than 96 hours after the onset of symptoms.

Table 5: Day of Presentation to the hospital

DAY OF PRESENTATION	No of PATIENTS
DAY 1	17
DAY 2	19
DAY 3	15
DAY 4	12
DAY 5	10
DAY 6	13
DAY 7	14

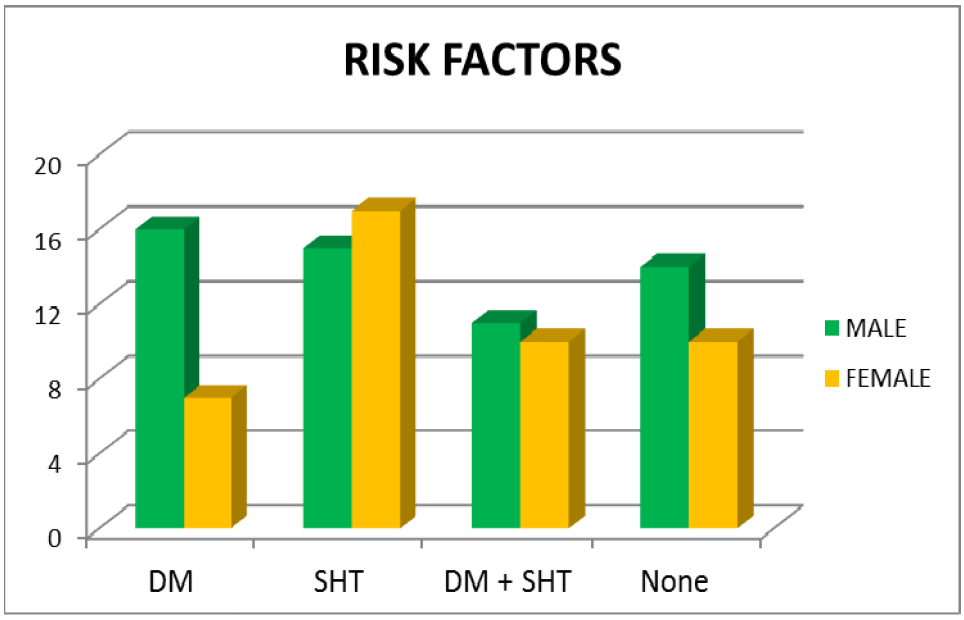

Figure 3: Prevalence of Diabetes and Hypertension

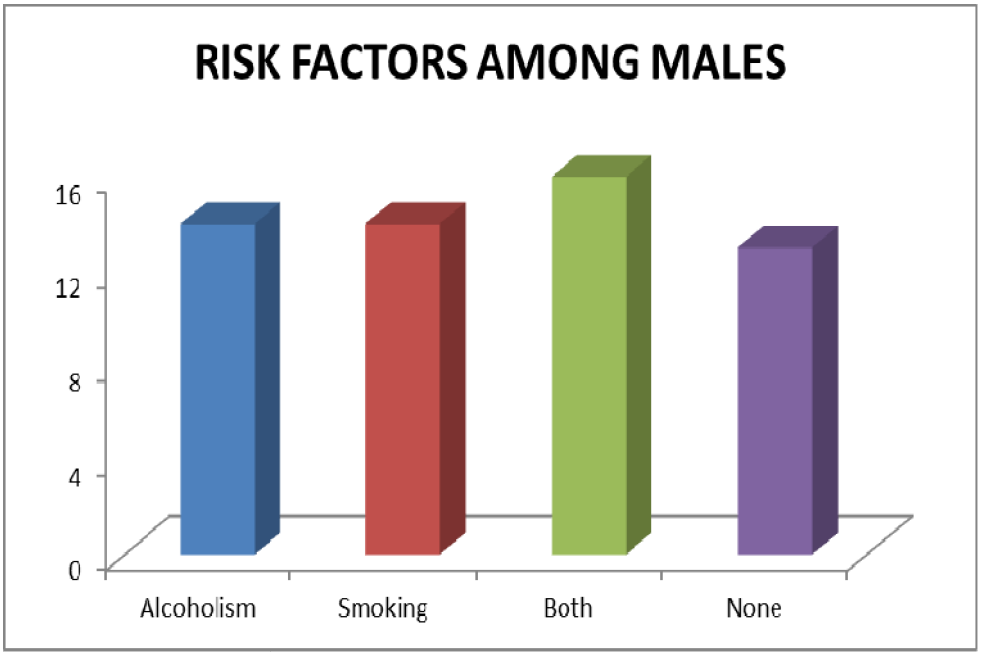

Figure 4: Prevalence of Risk factors among males study subjects

LESIONS INVOLVED

Infarcts/ haemorrhages

There was a large preponderance of arterial infarcts when compared to the haemorrhages (**Fig 5**). Only 23 patients had an intracerebral bleed whereas 77 of them had arterial infarcts (**Table 6**).

Arterial involvement

The middle cerebral artery (MCA) territory was most commonly involved (**Fig 6**) with 78 patients having either an infarct or haemorrhage there. While posterior circulation was involved in 18 patients, only 4 patients had involvement of anterior cerebral artery territory (**Table 7**).

Right vs. Left side

Forty six of the patients had involvement of the right side and forty eight patients had involvement of the left side while only six patients had bilateral involvement (**Table 8**). Among the patients with MCA territory involvement, 35 had right sided involvement while 43 patients had left sided involvement (**Fig. 8**).

Table 6: Lesion identified by radiological investigation

TYPE OF LESION	PATIENTS
Haemorrhage	23
Infarct	77

Table 7: Arterial territory involvement

ARTERIAL TERRITORY	PATIENTS
Anterior Cerebral Artery	4
Middle Cerebral Artery	78
Posterior Circulation	18

Table 8: Side involvement

SIDE OF LESION	PATIENTS
Right side	46
Left side	48
Both sides	6

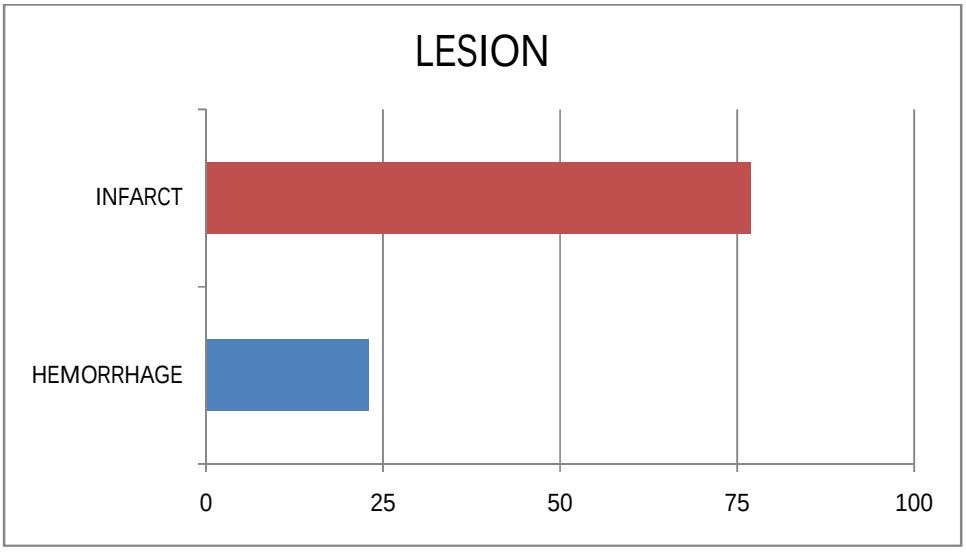

Figure 5: Lesion found by radiological investigation

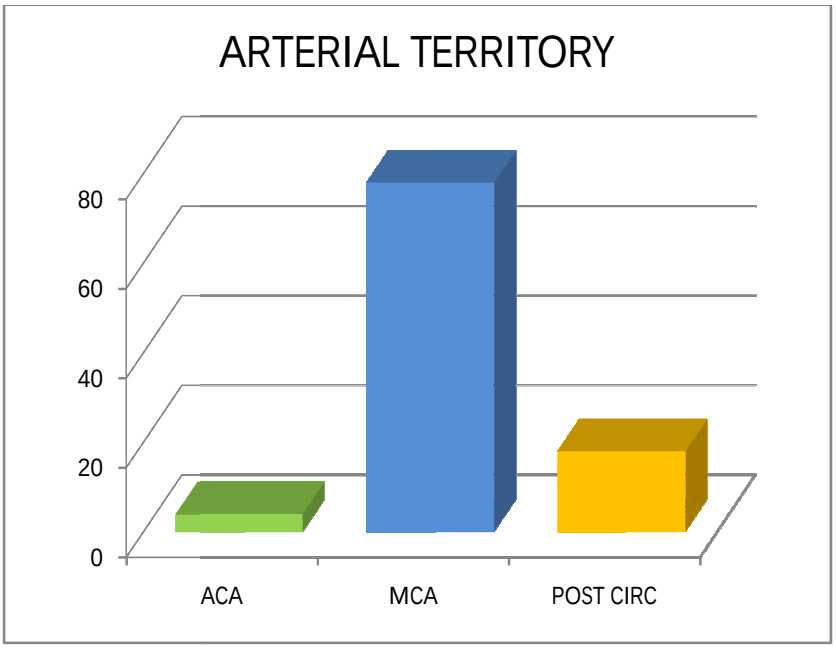

Figure 6: Arterial Territory involved

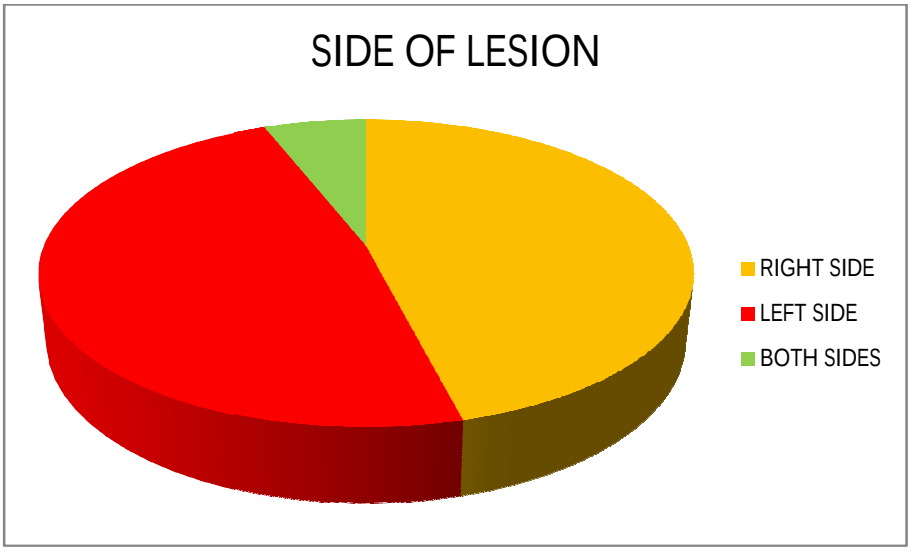

Figure 7: Side of the Lesion

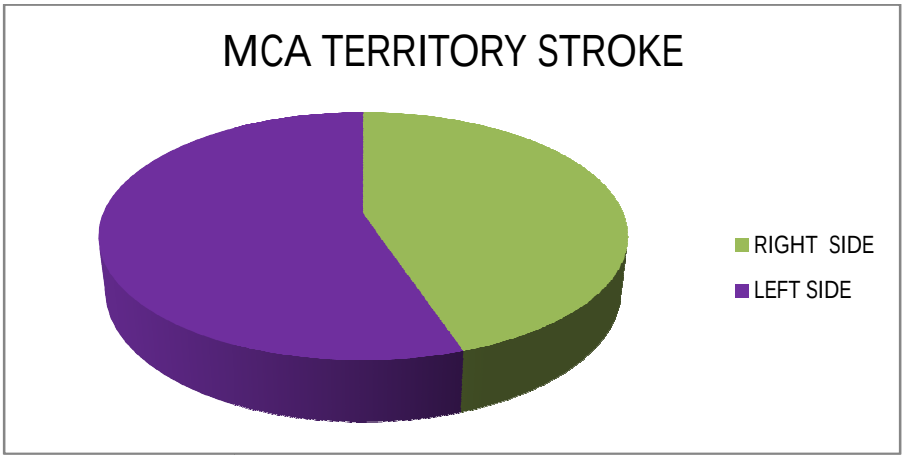

Figure 8: Side of the Lesion among MCA Lesions

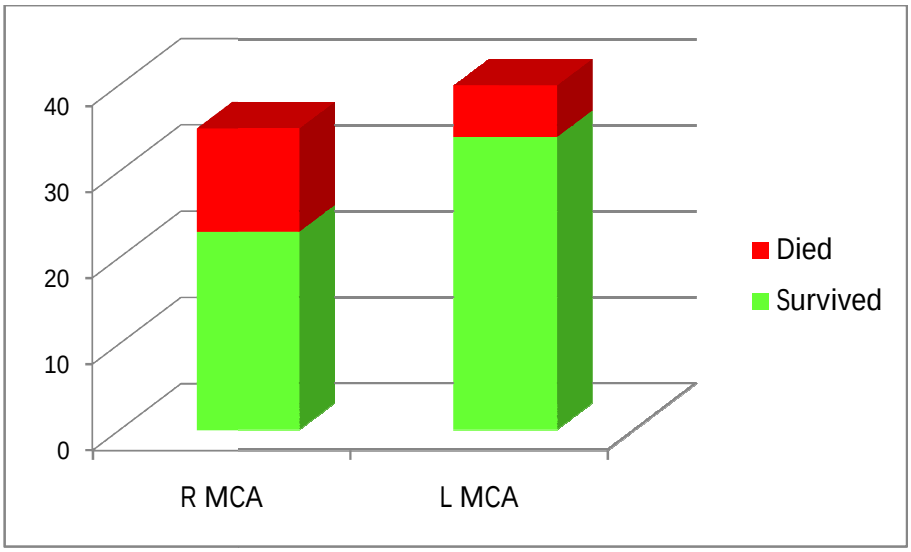

Figure 9: Effect of Side of MCA Territory on Survival

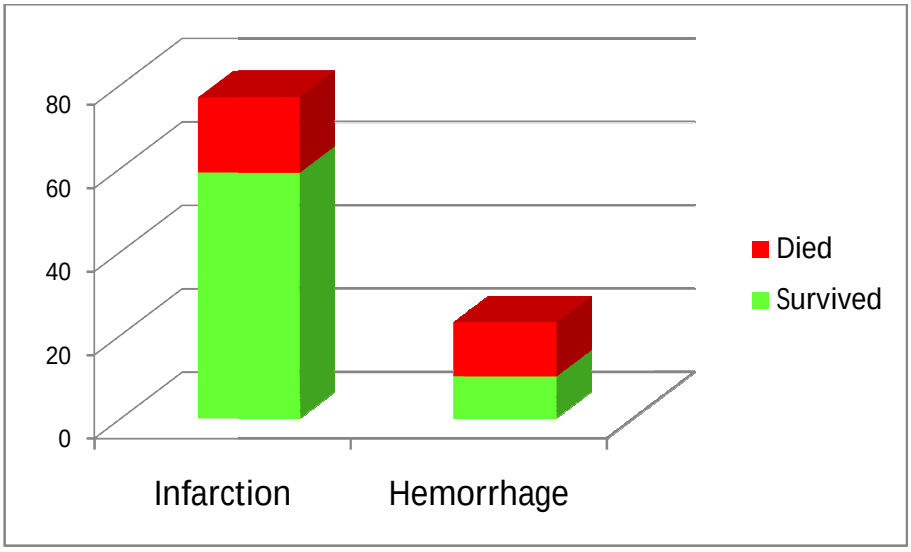

Figure 10: Effect of Lesion on Survival

IMPACT OF SYMPATHOVAGAL IMBALANCE

The impact of the presence of the sympathovagal imbalance was assessed by dividing the study population into two groups on the basis of the LF/HF ratio. One group (**Group 1**) included all the patients who had a LF/HF ratio above 1 and the other group (**Group 2)** included all the patients who had a LF/HF ratio less than 1. The following baseline characteristics were observed among the groups (**Table 9**).

Group 1 consisted of 63 patients while Group 2 had 37 patients. The mean age was 63.21 ± 13.39 years in Group 1 while it was 57.59 ± 13.85 years in Group 2. Using the unpaired t test for difference between means, the difference was found to be statistically significant difference *(P<0.05).*

The mean duration of diabetes among the diabetics in the study population was 10.0 years (Range 0.0 – 25.0, n=30) in Group 1 against 6.71 years (Range 1.0 – 18.0, n=14). Using the Mann Whitney test for difference between means of non-parametric data, the difference was found to be statistically insignificant. The mean duration of hypertension among the hypertensives in the study population was 8.13 years (Range 1.0 – 25.0, n=29) in Group 1 against 6.50 years (Range 1.0 – 20.0, n=24) which was also not found to be statistically insignificant.

Table 9: Baseline Characteristics of the study population

CHARACTERISTIC	GROUP 1	GROUP 2	p value
Number of patients	63	37	
Age *(in years)*	63.2 ± 13.4	57.6 ± 13.9	0.0485*
Duration of DM *(in years)*	10.0 (0.0 – 25.0)	6.7 (1.0 – 18.0)	0.1574#
Duration of SHT *(in years)*	8.1 (1.0 – 25.0)	6.5 (1.0 – 20.0)	0.0710#
Alcoholics*(n)*	23	8	0.1786#
Smokers*(n)*	20	10	0.6583#
Systolic BP *(mm Hg)*	167.6 ± 25.4	148.5 ± 19.4	0.0002***
Diastolic BP *(mm Hg)*	101.0 ± 18.9	88.8 ± 12.7	0.0007***
NIHSS Score	16.1 ± 8.3	11.5 ± 6.6	0.0045**
LF Power *(n. u.)*	63.05 ± 8.9	31.96 ± 10.6	<0.0001****
HF Power *(n. u.)*	35.33 ± 9.0	66.43 ± 10.1	<0.0001****
Survival*(n)*	38	31	0.0152*

* – SIGNIFICANT ($p < 0.05$), ** – VERY SIGNIFICANT ($p<0.01$), *** – HIGHLY SIGNIFICANT ($p<0.001$), **** – VERY HIGHLY SIGNIFICANT ($p<0.0001$), # – NOT SIGNIFICANT

Results are reported as Mean ± Standard deviation and as mean with range wherever applicable. Difference between means for parametric data was calculated using the student's unpaired t-test with two tailed p value. Difference between means for non-parametric data was calculated using Mann-Whitney test with two tailed p value. Difference between proportions was calculated using Fisher's exact test with two tailed p value.

The proportion of alcohol use among the patients of Group 1 was 36.51% (n = 23/63) against 21.62% (n = 8/37) in Group 2.

When the difference was analysed for significance using the Fisher's exact value test for proportions, the p value was found to be not statistically significant. The proportion of smoking among patients of Group 1 was 31.74% (n = 20/63) against 27.03 % (n = 10/37) in Group 2 and this difference was also found to be not statistically significant.

The mean systolic blood pressure recorded among the patients of Group 1 was found to be 167.6 ± 25.36 mm Hg versus 148.5 ± 19.42 mm Hg among the patients of Group 2 and this difference was highly significant *(P < 0.001)*. The mean diastolic blood pressure recorded among the patients of Group 1 was found to be 101.0 ± 18.94 mm Hg versus 88.76 ± 12.66 mm Hg among the patients of Group 2 and this was also found to be highly significant *(P < 0.001)*.

The mean National Institute of Health Stroke Scale score was found to be 16.14 ± 8.29 among patients of Group 1 while it was only 11.49 ± 6.63 which was also statistically very significant *(P <0.01)*. The mean spectral power of the low frequency component among patients of Group 1 was 63.05 ± 8.90 and among patients of Group 2 it was 31.96 ± 10.59. The mean

spectral power of the high frequency component among patients of Group 1 was 35.28 ± 8.96 and among patients of Group 2 it was 66.35 ± 10.12. Both the differences were statistically very highly significant with *P<0.0001*. The survival proportion was 60.32% (n=25/63) in Group 1 and 83.78% (n=6/37) in Group 2 and the difference was also found to be statistically significant *(P<0.05)*.

IMPACT OF LATERALIZATION OF THE LESION

A total of 78 patients had lesions involving the middle cerebral artery territory. Among them, thirty five of them had lesions on the right side while forty three of them had lesions on the left side (**Table 10**).

The mean systolic blood pressure was higher among the patients with right sided involvement when compared to the patients with left sided involvement (164.9 ± 23.74 vs. 154.6 ± 19.56 mm Hg) and this difference was statistically significant *(P<0.05)*. The mean diastolic blood pressure and the mean NIHSS score among the two groups were however not statistically significant.

The mean spectral power of the low frequency component and the mean LF/HF ratio was higher among patients with right sided involvement while the mean spectral power of the

high frequency component was higher among the patients with left sided involvement. All these differences were statistically very highly significant *(P<0.0001)*. However the survival proportions among the two groups was not statistically significant (65.71% among right sided lesions and 79.07% among left sided lesions).

TABLE 10: IMPACT OF RIGHT SIDE INVOLVEMENT VS. LEFT SIDE INVOLVEMENT AMONG PATIENTS WITH MIDDLE CEREBRAL ARTERY TERRITORY INVOLVEMENT

CHARACTER	RIGHT SIDE LESION	LEFT SIDE LESION	p value
No of Patients	35	43	
Systolic BP *(mm Hg)*	164.9 ± 23.7	154.6 ± 19.6	0.0389*
Diastolic BP *(mm Hg)*	99.0 ± 17.1	93.0 ± 15.0	0.1034#
NIHSS Score	14.4 ± 6.4	13.8 ± 7.5	0.7017#
LF Power*(n.u.)*	61.2 ± 13.8	43.2 ± 17.3	<0.0001****
HF Power*(n.u.)*	37.4 ± 13.7	55.0 ± 17.2	<0.0001****
LF/HF ratio	2.0 ± 1.0	1.0 ± 0.8	<0.0001****
Survival*(n)*	23	34	0.2089#

* – SIGNIFICANT (p < 0.05), ** – VERY SIGNIFICANT (p<0.01), *** – HIGHLY SIGNIFICANT (p<0.001), **** – VERY HIGHLY SIGNIFICANT (p<0.0001), # – NOT SIGNIFICANT

Results are reported as Mean ± Standard deviation and as mean with range wherever applicable. Difference between means for parametric data was calculated using the student's unpaired t-test with two tailed p value. Difference between means for non-parametric data was calculated using Mann-Whitney test with two tailed p value. Difference between proportions was calculated using Fisher's exact test with two tailed p value.

IMPACT OF THE TYPE OF LESION

In the one hundred patients studied, there was a predominance of infarcts, with only twenty three patients having a haemorrhagic lesion and the remaining seventy seven having an infarction (**Table 11**).

The mean systolic and diastolic blood pressures were much higher among the patients with haemorrhage when compared to patients with an infarction (178.20 ± 27.49 vs. 155.20 ± 21.75 and 108.70 ± 19.34 vs. 92.81 ± 15.73 mm Hg) and this difference was statistically very highly significant *(P < 0.0001)*.The mean NIHSS score was also higher among patients with haemorrhage when compared to those with infarctions, 20.48 ± 7.90 vs. 12.61 ± 7.14. This difference was also statistically very highly significant *(P < 0.0001)*.

The mean spectral power of the low frequency component and the mean LF/HF ratio was higher among patients with haemorrhage while the mean spectral power of the high frequency component was higher among the patients with left sided involvement. All these differences were statistically very highly significant *(P<0.0001)*. Also the survival proportions among the two groups was statistically very significant (43.48 %, n=10/23

among patients with haemorrhagic lesions and 76.62%, n=59/77 among patients with infarcts) *(P<0.01)*.

TABLE 11: IMPACT OF TYPE OF LESION AMONG ALL PATIENTS

CHARACTER	INFARCTION	HAEMORRHAGE	p value
No of Patients	77	23	
Systolic BP *(mm Hg)*	155.2 ± 21.8	178.2 ± 27.5	<0.0001****
Diastolic BP *(mm Hg)*	92.8 ± 15.7	108.7 ± 19.3	<0.0001****
NIHSS Score	12.6 ± 7.1	20.5 ± 8.0	<0.0001****
LF Power*(n.u.)*	48.7 ± 17.7	61.2 ± 15.1	0.0028***
HF Power*(n.u.)*	49.6 ± 17.5	37.3 ± 15.3	0.0031***
LF/HF ratio	1.3 ± 0.9	2.0 ± 1.1	0.0013***
Survival*(n)*	59	10	0.0043**

* – SIGNIFICANT (p < 0.05), ** – VERY SIGNIFICANT (p<0.01), *** – HIGHLY SIGNIFICANT (p<0.001), **** – VERY HIGHLY SIGNIFICANT (p<0.0001), # – NOT SIGNIFICANT

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IMPACT ON SURVIVAL

The impact of the heart rate variability on the outcome of patients with acute cerebrovascular disease was also assessed (**Fig9**). In patients who died, the mean power of the low frequency component and power of the high frequency component were higher and lower respectively and this difference was found to be statistically significant. The mean systolic and diastolic pressure and the NIHSS score were also statistically significant between the groups (**Table 12**).

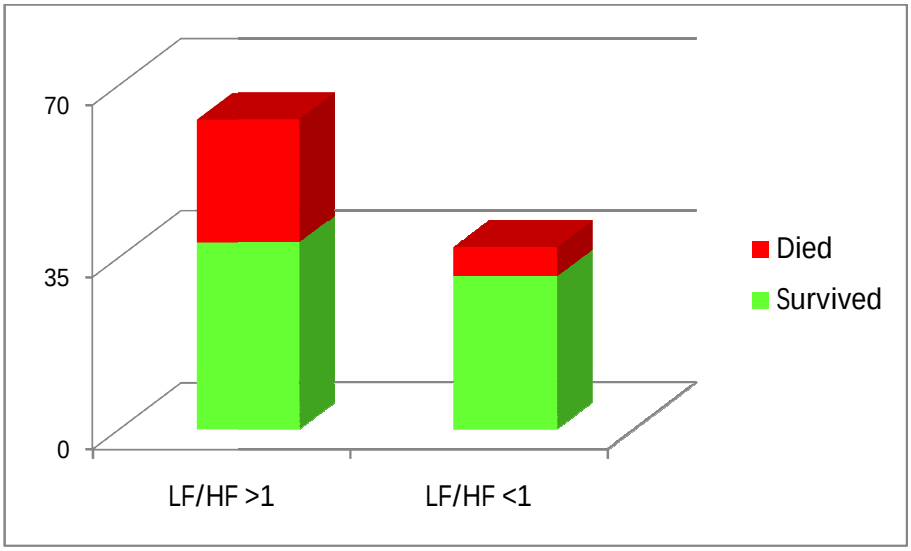

Figure 11: Effect of LF/HF Ratio on Survival

TABLE 12: IMPACT OF HEART RATE VARIABILITY ON SURVIVAL

CHARACTER	SURVIVED	DIED	p value
No of Patients	69	31	
Systolic BP *(mm Hg)*	155.4 ± 20.6	171. 9 ± 30.2	0.002**
Diastolic BP *(mm Hg)*	91.9 ± 14.3	106.6 ± 20.9	<0.0001****
NIHSS Score	11.8 ± 6.4	20.2 ± 8.3	<0.0001****
LF Power*(n.u.)*	47.1 ± 17.6	61.4 ± 14.3	0.0001***
HF Power*(n.u.)*	51.2 ± 17.4	37.0 ± 146	0.0002***
LF/HF ratio	1.2 ± 0.9	2.0 ± 1.1	<0.0001****

* – SIGNIFICANT ($p < 0.05$), ** – VERY SIGNIFICANT ($p<0.01$), *** – HIGHLY SIGNIFICANT ($p<0.001$), **** – VERY HIGHLY SIGNIFICANT ($p<0.0001$), # – NOT SIGNIFICANT

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DISCUSSION

DISCUSSION

The present study carried out to assess the status of autonomic function of patients when admitted to a tertiary care referral hospital in public sector, to our knowledge,is the first of its kind in acute setting in this part of the world.The mean age (61.2 years) of the patients enrolled in the present study is in line with that of the Trivandrum Stroke Registry, a population based survey(67 years[77]), and that of Feigin et al, from the review of data from fifteen population based stroke incidence studies (60.8 to 75.3 years for males and 66.6 to 78.0 years for females[78]).

The disease prevalence peaked in the 7th decade of life with nearly one third of patients belonging to that age group. This is also similar to the findings reported by the Trivandrum Stroke Registry[77].However the finding in the present study of 6% of the patients being less than 40 years of age was slightly higher than the figure of 3.8% reported by the Trivandrum Stroke Registry[77]and comparable to the findings of Das et al who reported a prevalence of 8.8% in another population based study from West Bengal[79].There was a predilection of males in this study which was not in line with the findings of Trivandrum Stroke Registry which reported a slightly higher level of incidence among the females[77].

The prevalence of risk factors for stroke like diabetes mellitus, hypertension (53 vs. 83%), smoking and alcohol habit were much lower in this study population when compared to figures reported from population based survey carried out by the Trivandrum Stroke Registry[77]. The prevalence of hypertension was only 53% in this study whereas it was much higher at 83% in their study. This figure is however in line with the findings of Strong et al who estimated that hypertension caused 54% of stroke mortality in low-income and middle-income countries[80]. Modifiable risk factors like smoking and alcohol continue to have a higher prevalence among patients with stroke and this is a necessary target of intervention if we were to reduce the morbidity and mortality associated with the disease in a developing country like India.

The study was carried out in a tertiary care referral hospital serving not only the entire state of Tamilnadu but also neighbouring areas in the states of Karnataka, Andhra Pradesh and Puducherry. The patients came to seek medical attention after a varying period of time. One third of patients sought medical attention within 48 hours of onset of symptoms whereas a nearly equal number sought medical attention only after 96 hours preferring to have a wait and watch policy for self-improvement of

symptoms. This finding stresses the need to educate the general population about the disease in general and the necessity to seek medical intervention at the earliest as timely medical help will definitely go a long way in reducing the morbidity and mortality associated with the disease.

There were a large number of cases with infarction on imaging studies when compared to haemorrhage. This figure is comparable to the findings of Das et al and Sridharan et al [77,79]. It also lies within the range of 67.3% to 80.5% for infarction and slightly above the range of 6.5% to 19.6% as reported by Feiginet al[78].The overall case fatality rate of 31%,especially withthe elderly above 75 years having more chances of dying, is in agreement with the findings of theTrivandrum Stroke Registry and the study by Feiginand co-workers. [78].

In order to assess the effect of the altered sympathovagal balance in patients with acute stroke, the patients were divided into two groups. As the low frequency component were usually indicative of the sympathetic function and the high frequency component of the parasympathetic function, it is assumed that patients with a LF/HF ratio above 1 have a predominance of the sympathetic discharges on the heart and those with a LF/HF ratio

below 1 have a predominance of parasympathetic discharges on the heart.

When compared in such a way, the patients with LF/HF ratio had a significantly higher systolic and diastolic blood pressure reflecting the effect of the sympathetic system on the blood pressure. These patients also had a statistically significant higher NIHSS score, elevated low frequency power and decreased high frequency power. The patients with a higher value for the ratio had a statistically reduced survival advantage.

When the impact of lateralisation of the lesion in the middle cerebral artery territory was assessed, there was a definite and statistically significant difference in the sympathovagal balance. There was a higher level of sympathetic outflow when the lesions involved the right cerebral hemisphere. There was also a corresponding increase in the parasympathetic outflow whenever the lesions involved the left cerebral hemisphere. These findings are similar to those of Colivicchi et al who showed a statistically significant difference between the involvements of right and left insular cortexes[81]. Meyer et al reported that when the systolic and diastolic blood pressure and heart rate were recorded during the first five days after stroke, sympathetic activity was significantly higher in insular than in non-insular infarction with concomitantly

elevated cardiovascular parameters in insular stroke patients. They also reported that the pathological activation of the sympathetic nervous system was most excessive in patients with the stroke involving the right sided insular cortex which they said indicated a hemispheric lateralization in autonomic activity which is mediated by the right-sided insular cortex[82]. Sander et al also state that the insular cortex in particular has an important role in the genesis of the pathological activation of the sympathetic nervous system and that the mechanism of cardiovascular instability following stroke relates to the loss of inhibition of the insular cortex and a reacting augmentation of the sympathetic tone. They also go on to state that sympathetic activation is lateralized following hemispheric brain infarction and accordingly, patients with a right-sided hemispheric infarction show a significantly diminished circadian blood pressure variation as compared with patients with left-sided hemispheric infarction. They also found that hemispheric lesions were associated with a significantly higher incidence of cardiac arrhythmias[83].

These findings have also been well established in experimental animal models of ischemia by Cechettoet al[84]. Oppenheimer et al demonstrated that the rat posterior insular cortex possesses cardiac chronotropic organization and therefore

may be involved in cortical mechanisms of sudden death when involved by lesions[85].

However these findings were however not supported by Korpelainen et al who do not accept the effect of lateralisation of the cortical lesion on the heart rate variability[86]. Barron et al also demonstrated that the heart rate variability can be influenced by lesion on both sides[39].

In a recent study by Hilz et al, the NIHSS score was found to correlate with the heart rate variability with a higher score leading to an 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. They also found that all autonomic changes put patients with more severe stroke at increasing risk of cardiovascular complications and poor outcome and that NIHSS scores are suited to predict risk of autonomic dysregulation and can be used as premonitory signs of autonomic failure[87]. In a study by Pradhan et al from NIMHANS, they found that HRV measurements are independent predictors of outcome in acute severe stroke[88].

Korpelainen et al found that the distorted heart rate variability is related to a poor outcome in patients with acute hemispheric brain infarction and suggest that the monitoring of the dynamics of heart rate variability might be a useful indicator of the outcome of cerebral infarction in the future[86].

The overall case fatality rate was 31% which the elderly above 75 years having more chances of dying. The case fatality of total strokes in Trivandrum Stroke Registry was 27.2%[77]. The figures from this study also did not vary beyond the range of 17% to 33% noted by Feiginet al[78]. The long term mortality is also higher in this population than the general population with a greater than two-fold relative risk of death for those patients surviving beyond 30 days as established by Hankey et al from the Perth Community Stoke Study[89]. They also found that the majority of deaths beyond 30 days are caused by non-stroke related events, in particular cardiac death[89]. The one year fatality rate is 31% for cerebral infarction and 37% for all-stroke causes as found by Thrift et al[90]. 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[91].

It has also been clearly established that abnormal autonomic control, measured by heart rate variability, is an independent predictor of death after myocardial infarction[13, 92]. Reduced heart rate variability has been consistently associated with increased risk of cardiac and overall mortality, and it is hypothesized that this is because of sudden arrhythmic death caused by autonomic imbalance[93].

The study has established that Heart Rate Variability is a strong predictor for mortality in patients with acute stroke and has a role in the assessment of every stroke patient and it reiterates the fact that routine evaluation of autonomic functions is mandatory in every stroke patient.

CONCLUSIONS

CONCLUSIONS

Thefollowing conclusions are made from this study

1. There is a strong association between heart rate variability and poor short term both ischemic and haemorrhagic stroke
2. There is a strong association between right sided middle cerebral artery territory stroke and increased sympathetic discharges
3. There is a strong association between left sided middle cerebral artery territory stroke and increased parasympathetic discharges
4. There is a strong association between increase in the sympathetic dischargesand haemorrhagic lesions.

The role of the right sided cortical lesions in influencing the sympathetic tone has been established. However the exact mechanisms by which autonomic derangement affects outcome have not yet been clearly elucidated and the proposed underlying mechanisms are so far mostly speculative with definitive evidence in human beings still lacking. To elucidate the clinical implications of this finding more studies involving

more number of patients are warranted. Interventions directed towards addressing the sympathovagal imbalance has been validated in conditions like post myocardial infarction patients and heart failure patients. Whether similar interventions directed at rectifying the altered sympathovagal balance by pharmacological or other mechanisms can change the course of acute stroke and whether they can translate into patient benefits remains to be elucidated by further studies. Nevertheless, it seems that heart rate variability should definitely become a therapeutic target in future acute stroke research.

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