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Loss of circadian rhythm of blood pressure following acute stroke

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Abstract

Background: Epidemiology of acute stroke in developing countries differs from that in the developed world, for example, the age at stroke, risk factors, subtypes of stroke and prognosis. Hypertension remains a dominant risk factor and prognostic indicator in patients with stroke in all communities. The risk of stroke is directly related to elevations of blood pressure. A number of clinical studies have shown that the control of hypertension leads to a reduction in the incidence of stroke in a community. However there is still considerable controversy surrounds the changes in blood pressure in various subtypes of strokes and problem of management of elevated BP after stroke. We studied the circadian rhythm of blood pressure in patients following acute stroke.

Methods: To study the circadian rhythm of blood pressure, fifty consecutive patients with an acute stroke who were admitted to medical emergency within 120 hours of onset were included in the study. After a detailed history and clinical examination, a continuous blood pressure monitor (Spacelab 90207) was attached on the side ipsilateral to intracranial lesion (unaffected arm). The blood pressure was recorded for 24 hours at 15 minutes interval during daytime (6.00 am–6.00 pm) and 20 minutes interval overnight (6 pm to 6 am).

Results: Risk factors for stroke in 50 patients included hypertension in 31(62%), diabetes mellitus in 4 (8%), smoking in 13 (26%) and previous history of transient ischemic attack in 7 (14%) patients. Mean systolic pressure and diastolic pressure at admission were higher in patients with hemorrhagic stroke -29 patients (177 ± 24 mmHg and 105 ± 19 mmHg respectively) compared to patients with ischemic strokes-21 patients (150 ± 36 mm Hg and 89 ± 18 mm Hg respectively, p value <0.01 in both comparisons). The normal diurnal variation in blood pressure (night time dipping of more than 10%) was abolished in 44 (88%) of patients. Out of 44 nondippers, 29 patients showed reverse dipping i.e. rise of BP during night time compared to day time levels. None of the risk factors, clinical or laboratory variables, type of stroke or blood pressure changes differed significantly between these two groups.

Conclusions: Therefore, we showed a pathologically reduced or abolished circadian BP variation after stroke. Absence of normal dipping results in a higher 24 hour blood pressure load and may have more target organ damage than those with normal diurnal variation of blood pressure.

Background

Epidemiology of acute stroke is different in developing countries from that in developed world. The age at stroke, risk factors, subtypes of stroke and prognosis are different in developing countries. In India, ischemic strokes constitute 70–75% while hemorrhagic strokes account for 20–25% of total cases [1]. However, hypertension remains a dominant risk factor and prognostic indicator in patients with stroke in all communities. The risk of stroke is directly related to elevations of blood pressure. A number of clinical studies have shown that control of hypertension leads to a reduction in the incidence of stroke in a community[2]. Control of hypertension is important for stroke prevention in all age groups. An increased reported incidence of intracerebral hemorrhage in India may be due to undetected and uncontrolled hypertension and a referral bias in a tertiary care center due to the surgical management of many of these patients.

Many studies have focused on the nature and extent of alterations of circadian blood pressure patterns after acute ischemic stroke while only a few studies have studied circadian rhythm of blood pressure in the patients with acute intracerebral hemorrhage[3,4]. The accurate measurement of blood pressure after an acute stroke is important because antihypertensive therapy may be considered in some patients. However, blood pressure may be falsely elevated or depressed immediately after a stroke depending on the level of consciousness, severity of neurological deficit and physical activity. Conventional recordings in the wards may therefore be unreliable or misleading, leading to inappropriate prescribing or withholding of the antihypertensive therapy.

To overcome this problem ambulatory blood pressure monitoring (ABPM) has been proposed as a method of obtaining an accurate clinical assessment. ABPM devices are increasingly being used in the assessment of hypertension but their value in patients after stroke has not been studied systematically. Various studies have shown different changes of circadian blood pressure patterns after stroke depending on the pathogenesis and location of stroke providing some prognostic and therapeutic implications[3,4]. Still, considerable controversy surrounds the changes in blood pressure in various subtypes of strokes and problem of management of elevated BP after stroke. Therefore, we studied the circadian rhythm of blood pressure in patients following acute stroke.

Methods

50 consecutive patients (age 75 years or younger) who were admitted after an acute stroke within 120 hours of its onset were included in the study. Definition of stroke was based on World Health Organisation criteria; rapidly developing clinical signs of focal and at times global loss of cerebral function with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. Patients with transient ischemic attacks, subarachnoid hemorrhage, cortical vein thrombosis or atrial fibrillation were excluded from the study. All patients had a detailed clinical examination, laboratory studies and a CT scan study of the brain on admission. As per our study protocol, patients who were receiving antihypertensive therapy at the time of admission to the hospital were maintained on the same medication for the duration of the study. No new antihypertensive medication was given during the study period. The Spacelab 90207 ambulatory oscillometric blood pressure monitor (ABPM) was attached at the time of admission. ABPM device was attached on the side ipsilateral to intracranial lesion after relevant difference between the two limbs was ruled out by conventional checks of blood pressure. The first reading obtained with the ABPM device was compared with immediately preceding and following manual measurements. The blood pressure was automatically recorded for 24 hours after application of the blood pressure monitor at 15 minutes interval during day time (6.00 a.m. – 6.00 p.m.) and 20 minutes interval overnight (6.00 p.m. – 6.00 a.m.). The mean daytime and nighttime BP were calculated and the values were analyzed to determine diurnal variation and any evidence of nocturnal fall of blood pressure. Patients were considered to have dipping if the mean arterial pressure (MAP) at night was less than 90% of MAP during daytime. The blood pressure changes were calculated and a relationship with risk factors and nature of stroke was studied. Patients were bedridden at the time of admission and were subjected to ambulatory blood pressure monitoring in that state only

Statistical comparisons between BP and heart rate measurements were made with unpaired 't' test and chi square test. A value of $p < 0.05$ was considered statistically significant.

Results

50 patients (26 males, 24 females; age 57.5 ± + 11.5 years with range 22–74 years) admitted with acute stroke (within 120 hours of onset) to the emergency department of PGIMER, Chandigarh were studied (Table 1). The stroke patients were subclassified into hemorrhagic stroke (29 patients, 58%) and ischemic stroke (21 patients, 42%) based on CT scan findings. Hypertension was the commonest risk factor (31 patients, 62%). Other risk factors included diabetes mellitus in 4 (8%), smoking in 13 (26%) and previous history of transient ischemic attack in 7 (14%) patients. The incidence of risk factors namely hypertension, diabetes mellitus, smoking, history of transient ischemic attacks and coronary artery disease did not differ significantly between patients with hemorrhagic

Table 1: Demographic and laboratory variables of patients with stroke

Variables	Total	Dippers	Nondippers	P value
No of patients	50	6(12%)	44(88%)	<0.001
Age (in years)	57.5 ± 11.5	67.2 ± 6.6	56.2 ± 11.5	<0.05
Sex (M:F)	26:24	2:4	24:20	NS
Previous hypertension	31(62%)	3(50%)	28(63.6%)	NS
Diabetes mellitus	4(8%)	1(16.7%)	3(6.8%)	NS
CAD*	6(12%)	0	6(13.6%)	NS
Smoking	13(26%)	0	13(29.6%)	NS
Previous TIA**	7(14%)	1(16.7%)	6(13.9%)	NS
Time between onset to ABPM (hours)	34.7 ± 17.7	32.3 ± 14.2	34.9 ± 18.3	NS
Altered sensorium at admission(numbers)	34(68%)	2(33.3%)	32(66.6%)	NS
Blood Sugar (mg%)	138 ± 48	139 ± 34	138 ± 49	NS
Serum Creatinine(mg%)	0.91 ± 0.2	0.84 ± 0.2	0.92 ± 0.22	NS
Site of lesion				
Cortical	23	3	20	NS
Thalamus	14	3	11	NS
Basal ganglia	25	2	23	NS
Pons	2	0	2	NS

* Coronary artery disease **Transient ischemic attack

and ischemic strokes. 81% (25 patients) of the patients with a history of hypertension were on antihypertensive medication prior to the development of stroke. In all the patients, who were treated too, also had an uncontrolled blood pressure as could be assessed from the previous medical records. This was attributed to a poor compliance.

Mean systolic blood pressure at admission in this study was 166 ± 32 mm Hg and it was higher in patients with hemorrhagic stroke (177 ± 24 mm Hg) compared to that with ischemic stroke (150 ± 36 mm Hg, $p < 0.01$) (Table 2). Similarly, mean diastolic blood pressure at admission was also higher in hemorrhagic group compared to ischemic subgroup (105 ± 19 mmHg vs 89 ± 18 mm Hg, $p < 0.01$). All parameters of blood pressure changes mon-

Table 2: Blood pressure changes in patients with stroke-hemorrhage versus infarct

Variable	Total (n = 50)	Hemorrhage (n = 29)	Infarct (n = 21)	P value
Admission BP				
Mean SBP*	165.5 ± 32	176.9 ± 24	149.8 ± 36	<0.01
Mean DBP**	98.1 ± 20	105.0 ± 19	88.6 ± 17.8	<0.01
24 hour BP				
Mean SBP	159.2 ± 25.8	169.6 ± 21.7	144.8 ± 24.4	<0.001
Mean DBP	95.7 ± 16.4	102.3 ± 16.1	86.4 ± 12.1	<0.001
Mean MAP***	115 ± 23.7	125.9 ± 16.5	101.2 ± 25.0	<0.001
Daytime BP				
Mean SBP	160.4 ± 26.2	171.1 ± 21.8	145.6 ± 24.9	<0.001
Mean DBP	95.7 ± 17.6	103.3 ± 15.7	85.3 ± 14.7	<0.001
Mean MAP	116.6 ± 18.8	125.4 ± 15.2	104.5 ± 16.6	<0.001
Nighttime BP				
Mean SBP	158.5 ± 28.3	168.7 ± 26.1	144.4 ± 13.2	<0.01
Mean DBP	95.4 ± 18.5	101.7 ± 19.1	86.1 ± 25.3	<0.01
Mean MAP	121.5 ± 30.8	128.6 ± 29.6	111.6 ± 13.3	NS

*Systolic blood pressure,** Diastolic blood pressure,***Mean blood pressure

itored under this study (mean, SBP, mean DBP, mean MAP) were significantly higher in patients with hemorrhagic stroke compared to those in ischemic stroke during day time, night time and total 24 hours. Admission SBP and DBP were higher in patients with history of prior hypertension (174 ± 32 mm Hg and 103 ± 21 mmHg respectively) than in patients without history of previous hypertension (152 ± 30 mm Hg and 91 ± 18 mm Hg respectively, p value < 0.05 in both comparisons). Admission SBP was positively correlated with age of the patient ($p < 0.005$) and negatively correlated with time after onset of stroke. The admission SBP or DBP was not influenced by previous history of coronary artery disease, smoking, diabetes mellitus, and transient ischemic attack at the time of admission.

The normal diurnal variation in blood pressure i.e. night time dipping was abolished in 44 (88%) of patients. This nondipping was seen equally in both hemorrhagic and ischemic subgroups without any statistically significant difference. Out of 44 nondippers, 23 patients showed reverse dipping i.e. rise of BP during nighttime compared to daytime levels. None of the risk factors, clinical or laboratory variables or blood pressure changes differed significantly between these two subgroups (Table 1,3). None of the patients had a recurrence of stroke during the study period.

Discussion

Hypertension is a well documented treatable single risk factor for stroke[5]. It is associated with an increased risk of all major subtypes of strokes. The reduction of blood pressure in primary prevention studies appears to reduce the relative risk of all types of stroke. The role of hypertension as a chief risk factor has been documented in Indian studies as well. The younger age of stroke in India studies has been stressed and is possibly related to a prolonged period of undetected untreated hypertension.

The development of devices capable of monitoring blood pressure noninvasively for 24 hours or more has been a major advance in blood pressure measurement. The large number of readings obtained by these devices reduces the variability and abolishes the observer bias encountered with casually recorded blood pressure[6]. Reducing variability also improves the precision with which blood pressure reduction can be quantified. ABPM devices have been used to assess the BP changes after stroke. Lip et al [6]studied the blood pressure variability in patients with acute stroke with oscillometric method and found that the readings comparable to those obtained with stethoscope and mercury manometer. ABPM increases the precision of recordings and minimize error compared to manual measurement. Many studies from western countries [3,4] are available on the use of ambulatory blood pressure monitoring devices in patients with acute stroke. However, to the best of our knowledge, this is the first study on the use of ABPM in stroke from India.

In contrast to normotensive patients or patients with primary hypertension, who show a biphasic circadian BP pattern with physiological nocturnal BP decreases in excess of 10%, a pathologically reduced or abolished circadian BP variation has been described after stroke. The significant reduction of circadian blood pressure variation after thromboembolic infarction was initially reported by Sander et al[3].

This study has clearly demonstrated that nondipping in blood pressure occurs in majority of patients with stroke irrespective of the underlying nature or site of stroke. However, the interpretation of the reduced day night difference or nondipping is complicated by some factors. 20% of the hypertensive patients exhibit nondipping[6]. The phenomenon has also been described in diverse medical conditions including renal disease, diabetes with autonomic neuropathy, heart failure and Cushing's syndrome. Though it is possible that abnormal diurnal variation in blood pressure existed in some of these patients due to co-morbid medical conditions like diabetes mellitus, coronary artery disease and previous transient ischemic attacks, it was not possible to predict or identify this subgroup of patients, as this study was prospective. Moreover, the sleep patterns in any patient population are highly variable. This, apart from the appreciable arousal from sleep on cuff inflation in some patients is another inherent limitation in all studies done on ABPM device. However in our study, the difference in the incidence of nondipping and dipping was highly significant and these factors can be discounted. Yamamoto et al[7] had proposed that the reduced nocturnal blood pressure decline might be associated not only with extent and type of the stroke but also with the specific location of intracranial lesion.

Diminished nocturnal blood pressure decline would be caused by an injury to the central autoimmune nervous system that reduces sympathetic activity during the night and increases parasympathetic activity. However we could not find any association with the site of stroke and status of dipping. None of the risk factors, clinical or laboratory variables or blood pressure changes differed significantly between the two subgroups of dippers and non-dippers. However, a reduction in diurnal change with thromboembolic infarction and the presence of a reversed dip in subjects with involvement of insular cortex has been reported[3]. Lip et al[6] have observed highest daytime blood pressure by ABPM and a trend toward higher nocturnal blood pressure in patients with intracranial hemorrhage. It has been reported that patients with involvement

Table 3: Blood pressure changes in patients with stroke-dippers versus nondippers

Variable	Total (n = 50)	Dippers (n = 6)	Nondippers (n = 44)	P value
24 hour Mean BP				
Mean SBP	159.2 ± 25.8	163.3 ± 11.2	158.6 ± 27.2	NS
Mean DBP	95.7 ± 16.4	93.5 ± 9.3	95.9 ± 1.2	NS
Mean MAP	115 ± 23.7	117.67 ± 8.6	115.3 ± 25.1	NS
Daytime BP				
Mean SBP	160.4 ± 26.2	177.7 ± 14.6	158.1 ± 26.7	NS
Mean DBP	95.7 ± 17.6	102 ± 11.0	95.0 ± 18.2	NS
Mean MAP	116.6 ± 18.8	128.5 ± 9.2	115 ± 19.4	NS
Nighttime BP				
Mean SBP	158.5 ± 28.3	148.5 ± 14.2	159.9 ± 29.5	NS
Mean DBP	95.4 ± 18.5	85 ± 11.5	96.5 ± 18.9	NS
Mean MAP	121.5 ± 30.8	106.2 ± 12.6	123.6 ± 32.0	NS
Admission BP				
Mean SBP	165.5 ± 32	177.5 ± 23	163.9 ± 33.4	NS
Mean DBP	98.1 ± 20	97 ± 18	98.3 ± 20.8	NS

of insular cortex show a nocturnal rise of blood pressure more frequently and had higher norepinephrine levels than patients without insular cortex infarction, indicating increased sympathetic activity in these patients. The lack of fall of blood pressure in acute phase may by due to an increased secretion of epinephrine and cortisol in the acute phase of stroke. We could not find such an association, as nondipping was present equally in both the subgroups, though the incidence was higher in patients with intracranial hemorrhage than those with infarct.

In this study, admission BP was higher in patients with a previous history of hypertension. Britton et al[8] have shown that a history of hypertension was common amongst patients of stroke than controls (46% vs 26%). Wallace et al[9] showed that the majority of stroke patients were hypertensive during the first 24 hours. Half of them had a history of hypertension or were on antihyhpertensive therapy. Patients with acute stroke often have high blood pressure levels at the time of hospital admission, but it declines soon afterwards. The reasons for this high blood pressure are not exactly known. Many investigators have found elevated levels of plasma catecholamines in acute phase of stroke, which may be secondary to the brain lesion[10]. Various factors responsible for an elevated blood pressure include a decreased perfusion in ischemic border zone, stress reaction to hospital admission, technique of blood pressure measurement, Cushing's reflex or white coat effect [11,12]. Morfis et al [4] showed that the transient elevation in blood pressure at admission did not appear to be due to stress of hospitalization since it was not present in patients admitted to hospital in a range of medical conditions other than stroke.

In our study, the average admission SBP was 166 ± 32 mm Hg and admission DBP was 98 ± 20 mm Hg. These values were higher in patients with intracranial hemorrhage than those with infarcts ($p < 0.01$). These findings are consistent with other studies. Admission SBP, in our study had shown a positive correlation with the age of the patient. Carlberg et al[13] also found a correlation of age with SBP, but not DBP at admission only in patients with hemorrhage. In our study the admission SBP or DBP was not influenced by previous history of coronary artery disease, smoking, diabetes mellitus, transient ischemic attack or level of consciousness at admission. Admission SBP and DBP showed a negative correlation to the time after the onset of stroke to the admission. The inclusion criterion in the present study was that the time period between the onset of stroke to the monitoring should be less than 120 hours. However, the mean time interval of application of ABPM after the stroke was only 35 ± 18 hrs (range 2–90 hrs). This was not statistically significant between dippers versus non-dippers thereby suggesting that the status of dipping was not related to the time of admission within this time interval. Rather a long time interval from the onset of stroke to the enrolment in the present study was planned at the time of the design of the study due to long and a delay in the transport of the patients from the remote areas to our tertiary care center.

In studies of patients with stroke, abnormal pattern of circadian rhythm of blood pressure using ambulatory blood pressure monitoring (ABPM) has been reported [3,7]. In a study, Dawson et al[14] found a significant reduction in diurnal variation in systolic blood pressure in cortical infarct and intracerebral hemorrhage subgroups, compared with control subjects. The subcortical infarct subgroup demonstrated only minimal reduction in normal circa-

dian variation. Fujishima et al[10] reported that blood pressure was elevated in the acute phase of a single lacunar infarction and it declined with time. No night time fall was noted in acute phase, but the circadian variation in blood pressure normalized in the subacute and chronic phase. Some studies done by ambulatory blood pressure monitoring in acute phase of stroke suggested that cerebrovascular diseases also cause a prognostically unfavorable suppression of heart rate variability[15]. Both the sympathetically and parasympathetically mediated components of heart rate variability are diminished as a consequence of acute stroke.

Conclusions

Our findings show that the normal diurnal variation in blood pressure i.e. night time dipping was abolished in both ischemic and hemorrhagic stroke with no significant relation to the site of stroke. Patients with intracerebral hemorrhage tend to have higher blood pressure measurements at admission. SBP was positively correlated with age of the patient and negatively correlated with time after onset of stroke. We could not assess the relation between outcome of stroke and status of dipping as none of our patients expired during the study. However, in view of suggested poor prognosis of nondippers and a significant incidence of nondipping and reverse dipping in our patients, it is proposed that patients with acute stroke require close monitoring of blood pressure especially at night.

Competing interests

None declared.

Authors' contributions

S Jain planned, wrote and supervised the execution of the study, K K N Namboodri did the Clinical aspect and performed CABP, S Kumari supervised, and S Prabhakar supervised and guided the writing aspect.

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