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AMBULATORY BLOOD PRESSURE PATTERN IN HEALTHY NORMOTENSIVE SUBJECTS

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In partial fulfillment of the requirements
For the award of the degree of

M.D in GENERAL MEDICINE

BY

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STRUCTURED ABSTRACT

Introduction: Ambulatory blood pressure monitoring helps in detecting masked hypertension and in understanding nocturnal blood pressure patterns in currently normotensive subjects. Studies on the ambulatory blood pressure patterns in currently healthy normotensives are lacking in Kerala.

Objectives: (1) This study was done to find out the prevalence of masked hypertension (2) To study normal daily blood pressure patterns in healthy normotensives (3) To find out mean 24-h systolic & diastolic BP variation with age group and sex (4) To find out the difference in ambulatory blood pressure patterns in normotensives with & without family history of hypertension in 1st degree relatives.

Methods: it was a cross sectional study on 100 healthy normotensive subjects in the age group 18-55 years who were the staff / students of government medical college Kozhikode over 1 year period (January 1st 2019 to December 31st 2019). 24hour ambulatory blood pressure monitoring was done in normotensive subjects who met the inclusion criteria.

Results: The prevalence of masked hypertension was 9.3%. The prevalence of dippers, non-dippers, reverse dippers and extreme dippers were 46.5%, 41.9%, 9.3% and 2.3% respectively. Nocturnal dipping pattern was found to have significant association with age group and family history of hypertension. While masked hypertension was found to have association with age and body mass index.

Conclusion: The present ABPM study in healthy normotensives shows that there is age and sex related differences in circadian BP patterns. Prevalence of masked hypertension in healthy normotensive subjects in the present study is 9.3%. Family history of hypertension had significant association with non-dipping pattern.

Keywords: Ambulatory blood pressure monitoring; masked hypertension; dipping; non-dipping; reverse dipping and extreme dipping.

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INTRODUCTION

Hypertension is a global public health issue (WHO). It is a cause of premature death worldwide. High blood pressure is the leading cause of cardiovascular disease risk factor globally. Cardiovascular disease accounts for approximately 17 million death a year, nearly one third of the total. Of these complications of hypertension accounts for 9.4 million death worldwide every year. Elevated blood pressures are responsible for 41% of death due to heart disease & 51% death due to stroke. It is attributable to 13% (9.4 million death/year) death globally. In India age standardised CVD death rate is higher than the global average. Cardiovascular diseases contributed 28·1% of the total deaths in India. (Global Burden of Disease 1990-2016).

Hypertension rarely causes symptoms in the early stages & many go undiagnosed. As the rule of halves says "only half of hypertensives are aware, only half of those aware are treated & only half of being treated are adequately kept under control". Classical definition of hypertension is based on office BP measurements. Office BP may be elevated when true BP is normal (white coat effect), or it may be normal when the true BP is elevated (masked hypertension).

Patients with masked hypertension have similar risks as those with hypertension, hence their treatment may lead to an overall reduction of cardiovascular events and thus in reduced burden for healthcare. According to Banegas et al greater mortality is associated with masked hypertension than with sustained hypertension. It might be due to the delayed detection of masked hypertension in patients, who consequently could have more organ damage and cardiovascular disease than patients with sustained hypertension.

ABPM provides a profile of blood pressures away from the medical environment which represents a more reliable assessment of actual BP than office BP. Shows BP behaviour over 24 h period during usual daily activities, rather than when patient is sitting in the artificial circumstance of a clinic or office. It eliminates observer bias. It can identify patients with blunted or absent BP reduction at night – the non-dippers who are at greater risk for end organ damage & cardiovascular morbidity. Loss of the nocturnal decline in BP (non- dipping pattern) has been associated with increased risk of cardiac, kidney, and vascular target organ injury compared with patients whose decline in BP at night is normal dippers.

OBJECTIVES

- To study normal daily blood pressure patterns in healthy normotensives.
- To find out mean 24-h systolic & diastolic BP variation with age group & sex.
- To find out the prevalence of masked hypertension.
- To find out difference in ambulatory blood pressure patterns in normotensives with & without family history of hypertension in 1st degree relatives.

BACKGROUND & REVIEW OF LITERATURE

Globally cardiovascular disease accounts for approximately 17 million deaths annually, nearly one third of the total. Of these, complications of hypertension account for 9.4 million deaths worldwide every year[1]. The Global Burden of Disease study estimate of age-standardized cardiovascular disease death rate shows that in India it is 272 per 100000 population which is higher than the global average of 235 per 100000 population[2]. Hypertension is one of the major risk factors for coronary artery disease, stroke, myocardial infarction, heart failure and chronic kidney disease and contributes to premature mortality and morbidity[1].

Hypertension is a silent killer because in the early stages it rarely causes symptoms. As a result, many go undiagnosed and ends up in complications[1]. Treatment of complications of hypertension needs costly interventions such as cardiac bypass surgery, carotid artery surgery and dialysis. Hence early detection, adequate treatment and good control of hypertension has enough economic as well as health benefits[3]. However, it is a modifiable risk factor, with nonpharmacological and pharmacological measures[3]. Optimal treatment of hypertension begins with diagnosing the disease properly[3]. Hence, blood pressure measurements are essential for physicians in the diagnosis and management of hypertension.[4]

HISTORICAL PERSPECTIVE OF BLOOD PRESSURE MONITORING

Blood pressure was first measured more than 250 years ago, since then it has been assumed to be a fluctuating phenomenon, but it has been always read by static measurements in the physician's office[5]. Over 100 years, office blood pressure monitoring has been used for the diagnosis and management of hypertension. In India diagnosis of hypertension is generally based on BP measurement in the clinic using a mercury sphygmomanometer. Office blood pressure has several limitations. Single office blood pressure does not represent patients true BP status due to several reasons those include infrequent office visits or it may liable to errors and misinterpretations as the blood pressure is a dynamic variable. Moreover, office BP cannot measure blood pressure during day today activities and during sleep. In order to overcome the limitations of the office blood pressure monitoring several methods have been developed to perform BP

measurement outside the physician's office. In the 1940s, self- measurement at home was introduced, and two decades later the first ambulatory blood pressure recording devices were developed. These devices have been improved, rendered more convenient, made automatic, and are now available for 24-h measurement during a patient's normal day. It has now been recognised that such measurement is more physiological and more accurate in diagnosing hypertension than clinic measurement. In addition, such monitoring are recognised to have special utility in assessing response to treatment. In the 1960s significant works were done by George Pickering and Maurice Sokolow, two methods now widely in practice are Home BP monitoring and 24hour ambulatory BP monitoring. The major factors which influence the choice of the method of BP monitoring are the availability and cost of the device.

Ambulatory BP measurement has proven to be a stronger predictor of cardiovascular mortality than office BP measurement[6,7]. Out-of-office BP monitoring which includes ambulatory or home blood pressure monitoring offers specific advantages over OBPM such that it is able to get the blood pressure measured in an non clinical set up which itself has proven to reduce the white coat effect that may lead to a reduction of unnecessary treatment and thus saving costs for healthcare. For this reason, the National Institute for Health and Care Excellence (NICE) in the UK, JNC and ESC has recommended the use of ABPM for standard clinical. 24- hour ambulatory blood pressure ≥130/80mmHg indicates hypertension (primary criterion)[6,8]. Daytime (awake) ambulatory blood pressure ≥135/85 mm Hg and night time (asleep) ≥120/70 mm Hg indicates hypertension[6].

ABPM reveals dynamic blood pressure variability over a 24-hr period, during routine daily activities, rather than when the individual is sitting in an artificial environment of an office/clinic[6]. ABPM also offers diagnostic insights into nocturnal patterns of blood pressure, such as dipping and non-dipping, reverse dipping, and excessive dipping, and the presence of nocturnal hypertension; although less attention is given to the nocturnal behaviour of blood pressure in clinical practice, the nocturnal patterns of blood pressure have particular

importance in assessing the response to anti- hypertensive medication[9]. It also demonstrates the periods of decreased blood pressure over a 24 hour period[10].

The 2017 ACC/AHA guidelines have defined corresponding values of BP based on mode of measurement (office BP vs ambulatory BP) and the time of recording BP (day vs night time)[11] (table 1). For example, a BP of 120/80 mm Hg in a clinic setting is corresponding to an equal value of 120/ 80 mmHg in a daytime ABPM reading, 100/65 mm Hg in a night- time ABPM reading and 115/75 mm Hg in a 24-h ABPM reading. Similarly, BP of 130/80 mm Hg (stage 1 hypertension) based on office readings corresponds to an equal value of 130/80 mm Hg in a daytime ABPM record, 110/65 mm Hg in night time ABPM record.

As per the ACC/AHA 2017 guidelines, a normotensive patient should have a daytime ABPM <120/80 mm Hg and a night time ABPM < 100/65 mm Hg.[4] Absolute values for ambulatory BP thresholds are lower than those for clinic or office BP. Thresholds including a 24-hour average of ≥130/80 mm Hg, day- time average of ≥135/85 mm Hg, and night time average of ≥120/70 mm Hg are widely accepted and are supported by outcome data.[11]

Table 1: Clinic BP and Ambulatory BP

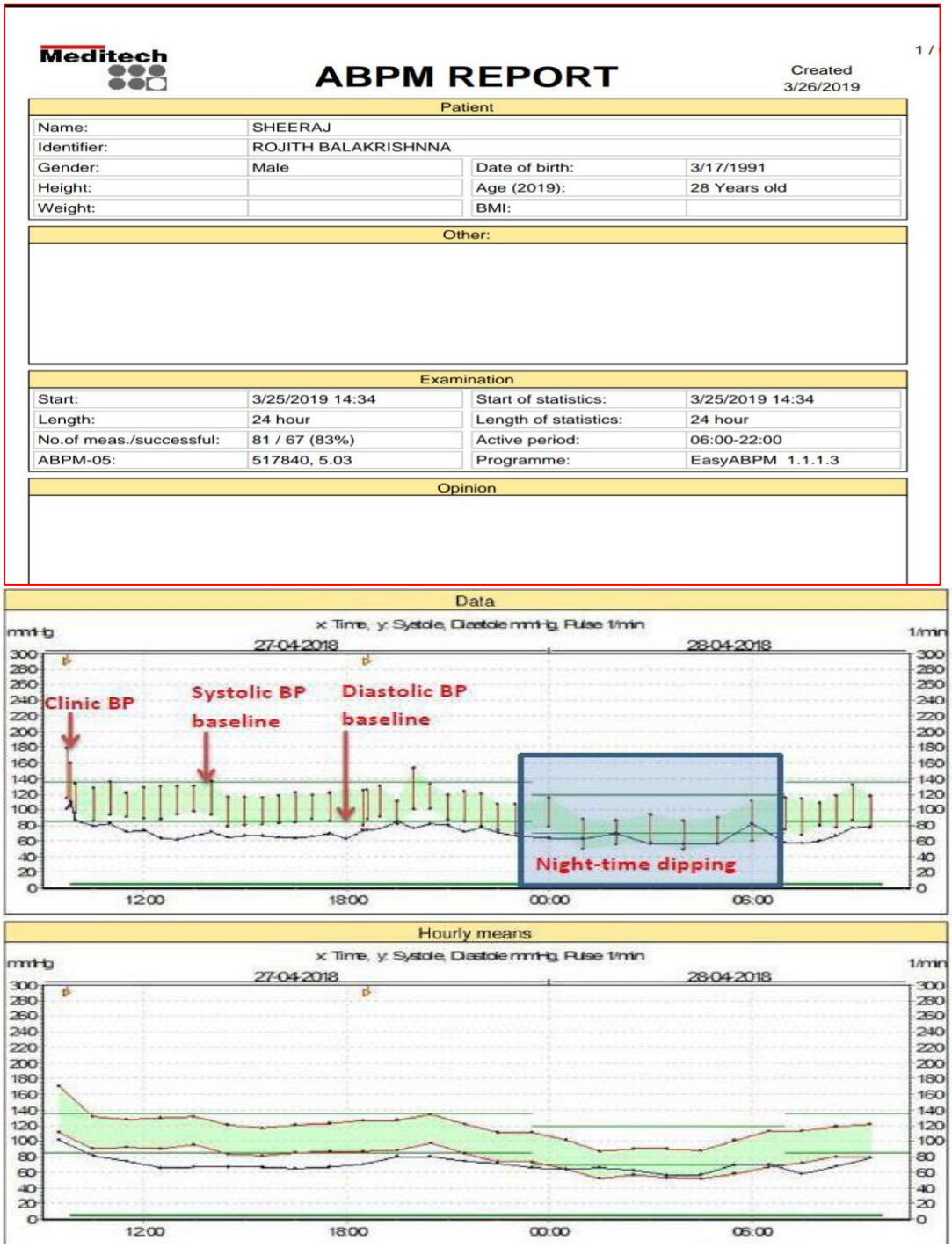
ClinicBP (mmHg)	Ambulatory BP (mmHg)			
	Daytime	**Night time**	**24hour**	**Morning**
120/80	120/80	100/65	115/75	120/80
130/80	130/80	110/65	125/75	130/80
140/90	135/85	120/70	130/80	135/85
160/100	145/90	140/85	145/90	145/90

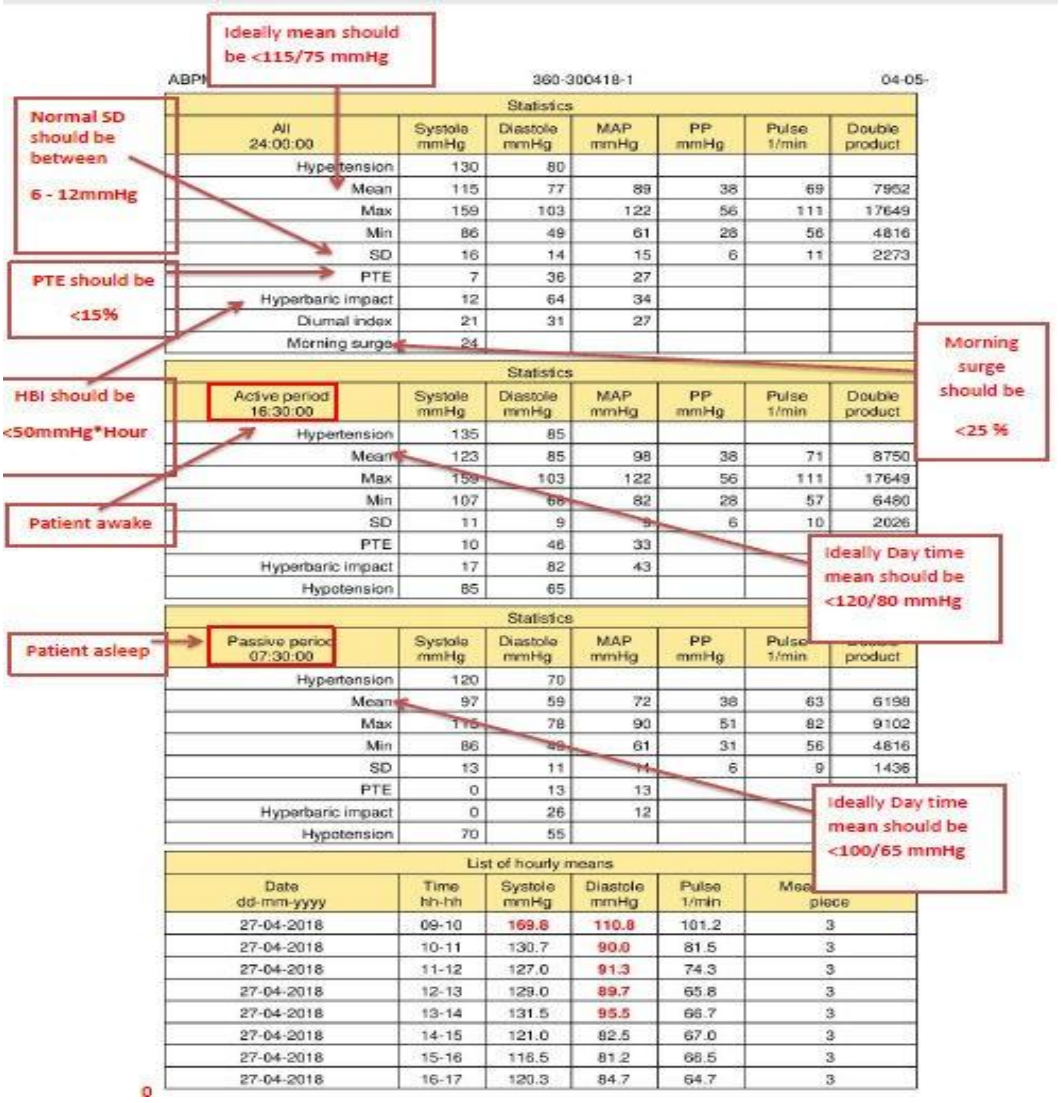
AMBULATORY BLOOD PRESSURE MONITORING

It refers to BP recording over 24 hours, to determine the blood pressure variability patterns. It is a more precise tool to detect the circadian changes (diurnal rhythmic changes, including nocturnal dipping and morning surge) and BP

variation with different environmental and emotional changes[4]. During 24 hour ABPM minimum readings required is 21 daytime & 7 night time readings. More than 80% successful readings are essential for an ABPM report to be conclusive. If less than 80% ABPM report is invalid and one should repeat the ABPM.

Figure 1: ABPM report





ABPM INDICES

MEAN BP: Average BP during 24hour period.

MAXIMUM & MINIMUM: Blood pressure and heart rate: gives the highest and lowest measured BP and heart rate values

STANDARD DEVIATION: amount by which each value deviates from the mean. Normal mean should be between 6-12mmHg. The standard deviation gives idea about the blood pressure variability of the patient. If standard deviation >12mmHg it indicates high blood pressure variability.

PTE (percent time elevation): It is the proportion of time during which blood pressure values are higher than systolic and diastolic BP considered to be normal. PTE > 50% indicates target organ damage.

HYPERBARIC (HBI) indicates the BP load on various organs. It is the area of the ABPM graph that exceed baseline for systolic and diastolic blood pressure. Studies has shown that HBI is a sensitive indicator for reduction in renal function. HBI >50mmHg indicates pressure overload.

DIPPING/DIURNAL INDEX is another index indicative of underlying target organ damage or inappropriate antihypertensive treatment. It describes the difference of mean BP (%) between awake and sleep periods. Calculated by dividing the difference between day and night time mean BP, respectively, by mean daytime BP and multiplying the resultant value by 100[4].

MORNING SURGE: It is basically a normal rise from a lower night blood pressure level to a somewhat higher day blood pressure level. Morning surge should be <25%. It is the difference in systolic blood pressure during the first two hours after awakening and the lowest level recorded during the night.

Normal diurnal BP variation

The phenomenon of diurnal variation in BP is well recognized[12,13]. Usually, BP start to rapidly rises on awakening in the early morning, reaches a plateau during the morning, falls slightly in the early afternoon and rises again in the early evening[12]. BP decreases gradually in the late evening, drops sharply after falling asleep and is lowest during sleep. These changes in BP are largely attributed to mental and physical activities, and the sympathetic nervous system has a crucial role in the generation of diurnal BP variation[12].

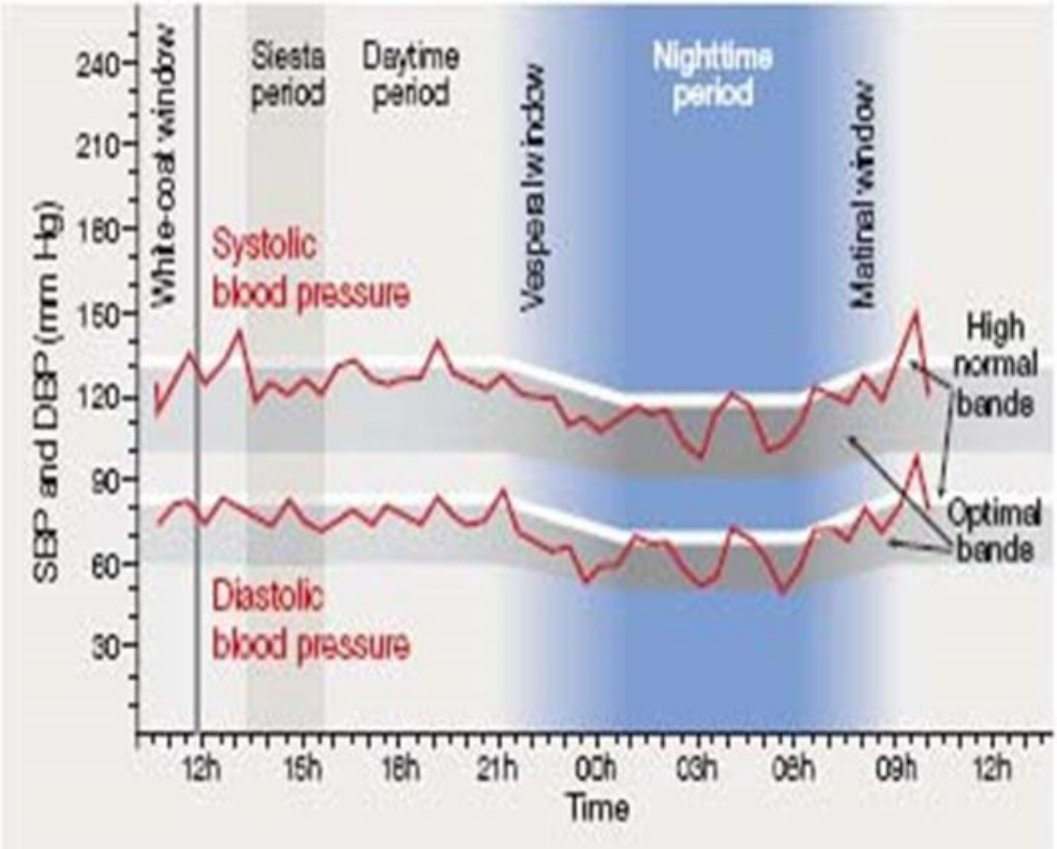


Figure 2: Normal diurnal BP variation

Clinical studies of healthy subjects and patients with spinal injuries have found that autonomic nervous system has a direct role in the regulation of the circadian variability of BP[1415]. It was seen that, in neurologically intact patients with lower spinal cord injuries, BP increased independently of activity but not in patients with sympathetic decentralization or higher spinal cord injuries. This sympathetic nervous system contributes to the regulation of BP over the 24-h period. Elevated resting measurements of sympathetic nerve activity were associated with greater daytime BP variability and a more marked nocturnal decline in BP in healthy normotensive subjects[15]. The renin–angiotensin–aldosterone system (RAAS), mainly via production of angiotensin II, is a key regulator of BP. The RAAS is activated in the early morning before waking up as a result of sympathetic neuronal activation. Both renin and aldosterone show significant circadian patterns in both normotensive and hypertensive individuals, with peak values detected early morning then falling to their minimum point in late evening. This pattern has also been observed for angiotensin II[15].

The early morning hours during the time of awakening, where an upright posture is assumed and activities of daily living begins, are associated with a pronounced rise in plasma catecholamine levels[16]. Catecholamines causes coronary vascular tone to increase, decrease vessel caliber, and have positive inotropic and chronotropic effects on the heart[17]. At the same time of day, plasma cortisol rises (which enhances vascular sensitivity to catecholamines), an increase in platelet aggregability, and an increase in blood viscosity, which is due to the tissue plasminogen activator. These factors, along with the increase in BP and HR, combine to enhance myocardial oxygen demand, diminish myocardial oxygen supply, and promote a hypercoagulable state[18]. These may be the principle physiologic foundations underlying the increase in cardiovascular and cerebrovascular adverse events observed during the morning[12].

There are three clinically significant consequences of nocturnal decline in BP First, the lower the nocturnal BP nadir, the more pronounced the morning surge. Second, there is concern that patients especially the elderly who have an extreme nocturnal fall in BP (extreme dippers) have more cerebral ischemia, resulting in the Binswanger's lesions, cerebral lacunae, and periventricular hyper lucencies seen on magnetic resonance imaging of the brain. Third, excessively low nocturnal BP can result in other ischemic phenomena, the most recently recognized of which are ophthalmic problems, such as anterior ischemic optic neuropathy.[17,19]

It has been shown that diurnal changes in BP coincide with changes in heart rate and the levels of plasma and urinary catecholamines. It was also found that BP is high during night time working hours and low during daytime sleeping hours in shift workers, although the dip in BP during sleeping hours may be attenuated at the beginning of the night shift. These findings suggest that the endogenous clock has a minor role in the generation of BP variation associated with the awake and sleep cycle. The morning rise in BP mainly depends on physical activity after waking. It has been shown that BP changes little after waking when the subjects remain supine, but rises rapidly when they get out of bed. It is also reported that the magnitude of the morning rise in BP is correlated with changes in physical activity.

Although the morning rise in BP is a physiological phenomenon, some hypertensive patients show an exaggerated rise in BP that is called the morning surge. Cardiovascular events such as myocardial infarction and stroke occur most frequently in the early morning, and the morning surge in BP appears to have an important role in the onset of these cardiovascular events[20]. On the other hand, the night time dip in BP is also altered in many hypertensive patients. A number of studies have shown that non dipping of the night time BP is associated with target organ damage and cardiovascular disease in hypertensive patients[21,12]

NOCTURNAL BP PATTERN

The Dublin Outcome Study conducted in 2005, done in 5292 untreated hypertensive patients who had clinic and ambulatory blood pressure measurement at baseline. Study was to determine if ambulatory blood pressure measurement predicted total and cardiovascular mortality over and beyond clinic blood pressure measurement and other cardiovascular risk factors. The patients were followed up in a prospective study of mortality outcome. There were 646 deaths (of which 389 were cardiovascular) during a median follow-up period of 8.4 years. With adjustment for gender, age, risk indices, and clinic blood pressure, higher mean values of ambulatory blood pressure were independent predictors for cardiovascular mortality. The study concluded that ambulatory measurement of blood pressure is superior to clinic measurement in predicting cardiovascular mortality, and night time blood pressure is the most potent predictor of outcome[22].

Night time BP will not be affected by environmental factors like wake up BP measurements[11]. Therefore it provides the most accurate representation of the BP phenotype of an individual. ABPM is the method of choice for studying night time BP[11]. Spanish study confirms that nocturnal BP is superior to all other measurements in predicting cardiovascular outcome[22].

The night-to-day BP ratio represents the ratio between average night-time and daytime BP[23,8]. BP normally decreases during the night—defined as dipping. The finding of a nocturnal BP fall of 10% of daytime values (night–day BP ratio,0.9) is known as dipping and those subjects are defined as ‘dippers’.

Or in other words, the expected physiological fall in night time BP is ≧10% known as dipping pattern. Dippers had a ≥10% but <20% fall in night BP. A reduction of <10% in BP at night is defined as non-dipping. Non- dippers have a night time BP fall <10% but >0%. Extreme dipping refers to patients who show a marked nocturnal fall (≧20%) in systolic and/or diastolic BP, or have a night/day systolic or diastolic BP ratio of <0.8. Riser, or reverse dipping, pattern show an increase in BP during sleeping hours to levels that may be higher than those during the day.

Possible reasons for absence of dipping are sleep disturbance, obstructive sleep apnoea, obesity, high salt intake in salt sensitive subjects, orthostatic hypotension, autonomic dysfunction, chronic kidney disease (CKD), diabetic neuropathy and old age.

Several studies have shown that hypertensive patients' left ventricular hypertrophy, increased carotid intima-media thickness and other markers of organ damage correlate with ambulatory BP more than with office BP. Furthermore, 24-h average BP has been consistently shown to have a stronger relationship with morbid or fatal events than office BP[24]. Ambulatory BP is considered to be a more sensitive risk predictor of clinical CV outcomes than office BP by evidences from meta-analyses of published observational studies. The superiority of ambulatory BP has been shown in the general population, in young and old, in men and women, in untreated and treated hypertensive patients, in patients at high risk and in patients with CV or renal disease. Several studies show that night-time BP is a stronger predictor than daytime BP. The night–day ratio is a significant predictor of clinical CV outcomes and gives prognostic information over and above 24-h BP.

With regard to the dipping pattern, the most consistent finding is that the incidence of CV events is higher in patients with a lesser or no drop in nocturnal BP than in those with greater drop. Extreme dippers may have an increased risk for stroke. However, data on the increased CV risk in extreme dippers are inconsistent and thus the clinical significance of this phenomenon is uncertain[8].

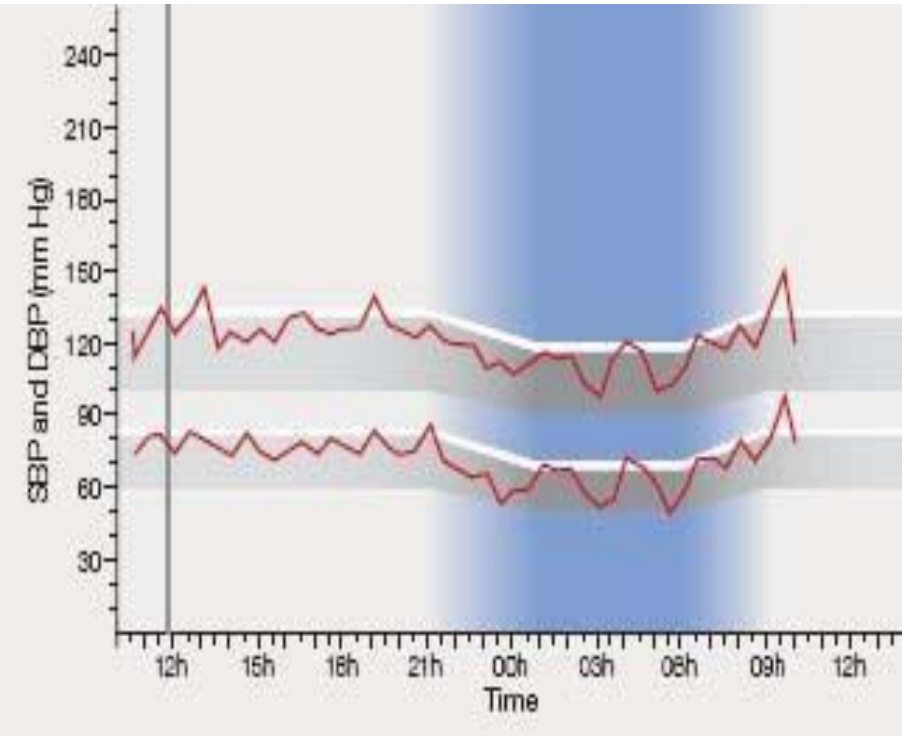


Figure 3: Normal dipping

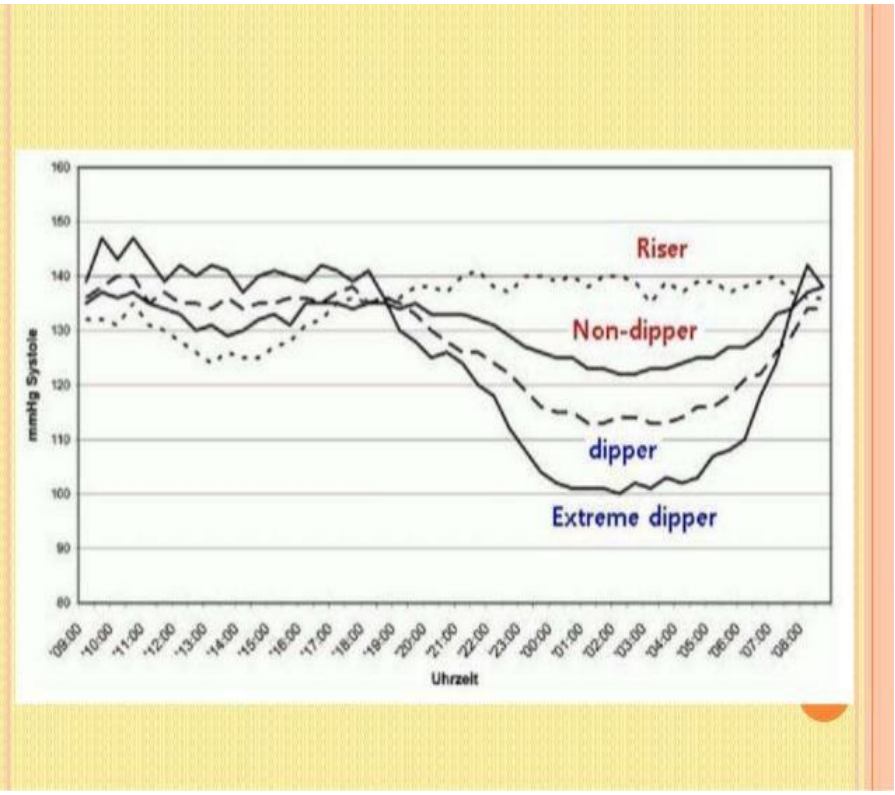


Figure 4: Dipping patterns

A study was conducted by Vaidya et al in Ravishankar Shukla university Raipur INDIA in 2012 about circadian variability and nocturnal dipping pattern of blood pressure in young healthy subjects using ambulatory blood pressure machine[25]. Sixty females and 40 males voluntarily participated in the study. All subjects wore an Ambulatory Blood Pressure Monitor (ABPM, TM 2430) for two to four consecutive days. Prevalence of extreme dipper, dipper and non- dipper was 13%, 63% and 24%, respectively. Study found out that variability in BP may be associated with factor gender to some extent, whereas nocturnal dipping in BP is independent of gender. Interestingly in the study about 24% subjects are non-dippers, which may be an indication of higher risk of cardiovascular diseases among individuals belonging to younger generation of this region.

NON -DIPPERS

In a cross-sectional study conducted in 1998, in the Miyori district in the rural community of Kinugawa by Hoshida et al in using ambulatory blood pressure (BP) monitoring, echocardiography, and carotid ultra- sonography and measured natriuretic peptides and urinary albumin in 74 normotensive subjects to investigate whether a non-dipper status was associated with target organ damage in normotensives[26]. The study concluded that the normotensive subjects who exhibited a non-dipping pattern of nocturnal BP had more advanced LVM and LV remodelling with increased cardiac natriuretic hormones than dippers. The study also found out that in normotensives, the absence of a nocturnal BP decrease might be independently associated with target organ damage, as there were no significant differences in office BP levels and 24-h BP levels between the dipper and non-dipper groups.

A number of studies have shown blunted night time BP dipping to be associated with target organ damage[11,27,28]. In untreated normotensive Japanese subjects, those with a blunted fall in night time BP demonstrated signs of cardiac overload vs those who showed a normal fall in night time BP[11]. A non-dipping night time BP pattern was associated with asymptomatic cerebrovascular disease in elderly hypertensive patients; both silent cerebral infarcts and deep white matter lesions were detected on brain magnetic resonance imaging[29]. Furthermore,

kidney damage has been reported in patients with a non-dipping pattern of BP and a non- dipping BP pattern was shown to be an important predictor of cardiovascular events and mortality in patients with end-stage renal disease[11].

Loss of the nocturnal decline in BP has been associated with increased risk of cardiac, kidney, and vascular target organ injury compared with patients whose decline in BP at night is normal[15]. Additionally, patients with hypertension who exhibit a nocturnal BP increase compared with daytime BP (risers) have the worst prognosis for stroke and cardiac events, with the rate being more in reverse dippers than in non-dippers[4,30]. However, there is also some evidence that patients with marked nocturnal BP declines (extreme dippers) are at risk of lacunar strokes and silent myocardial ischemia[15]. Studies that have assessed the impact of elevated nocturnal BP on the kidney have found similar results to those analyses of cardiac and cerebrovascular target organ involvement[15]. Non-dipping is different from nocturnal hypertension, which is an elevation of night time BP, whereas non-dipping arises because of improper control and regulation mechanism of BP. Non-dipping and reverse dipping have been shown to be associated with more organ damage, including left ventricular hypertrophy, cerebrovascular accident and renal disorders, with the rate being more in reverse dippers than in non-dippers[4]. Nocturnal dipping in BP is an important predictive factor of heart failure[31]. The level of BP is decreased considerably during sleep period and suddenly elevates during early morning hours resulting in cardiac surge. But in the case of non-dipping the BP remains elevated during the sleep period also, which is a higher risk of cardiovascular events. It has been documented that non-dipping in nocturnal BP is an independent predictor of higher risk of target organ damage and increased brain and cardiac complications among hypertensive individuals. Therefore, it is suggested that measuring BP with the help of ABPM for at least 24-h duration in hypertensive patients may provide beneficial outcome.

EXTREME DIPPERS

Extreme dippers have been known to have increased stroke rates[4]. A Japanese study found a 20% increase in cardiovascular mortality for every 5% attenuation in nocturnal BP fall, independent of overall 24 h BP[32]. Extreme dipping

(characterized by a ≧20% fall in nocturnal BP on ABPM) has been associated with stroke[33]. Data from the JMS-ABPM study showed that elderly hypertensive patients with an extreme-dipper pattern were at increased risk of future clinical stroke events[11]. Similarly, another study showed that extreme dipping was associated with a significant increase in the risk of intracerebral haemorrhage compared to patients with a physiological fall in night time BP[11]. In a meta-analysis of data from 17,312 patients with hypertension across three continents, the Ambulatory Blood pressure Collaboration in patients with Hypertension (ABC-H) found that an extreme-dipper pattern was significantly associated with cardiovascular events only in unmedicated patients[11,34,35].

MORNING BP SURGE

In the early morning, BP rises sharply in response to the natural activation of the sympathetic nervous system on morning arousal[15]. This early morning surge is also associated with other important hemodynamic and neurohormonal changes, such as increase in heart rate, vascular tone and blood viscosity, and decrease in vagal activity. The activity of the sympathetic nervous system appears to be downregulated during the rapid eye movement period of sleep, whereas awakening selectively stimulates the sympathoadrenal branch of the sympathetic nervous system and increases epinephrine levels. However, the increases in BP and heart rate are controlled by direct sympathetic neural input into the heart and vasculature in response to changes in activity and posture, rather than by an endogenous surge of plasma catecholamines[15]. Excess surge is known to be associated with stroke, myocardial infarction and sudden death[4].

The early morning BP surge period is associated with an increase in the incidence of cardiovascular events, including stroke and myocardial infarction[15]. Approximately one in every 11 myocardial infarctions, one in every 15 sudden deaths, and one in every 8 strokes being associated with the 'morning excess'[15,36]. Early morning BP surge is associated with an increased risk of cardiovascular and cerebrovascular adverse events, especially haemorrhagic stroke[11,37].

Markers of hypertensive heart disease, including increased left ventricular mass index, left ventricular hypertrophy, and a lower A/E ratio (a measure of

diastolic dysfunction), have all been associated with an exaggerated morning BP surge[11]. Significant relationships have also been reported between increased morning BP surge and both increased carotid intima-media thickness and microvascular dysfunction[11]. Vascular function, assessed using pulse wave velocity, has been shown to be impaired in patients with exaggerated morning BP surge[11]. Histologic data suggest that exaggerated morning BP surge accelerates the formation of atherosclerotic plaques and induces plaque instability as a result of vascular inflammation[38]. In the JMS-ABPM study, morning BP surge in the highest quartile was significantly correlated with levels of the inflammatory marker high- sensitivity C-reactive protein[39,40]. Asymptomatic cerebral infarcts are important surrogate markers for the occurrence of stroke, especially in the presence of increased CRP levels. In the JMS-ABPM study, a significantly higher proportion of patients with and without exaggerated morning BP surge and high sensitivity- CRP levels above the median had asymptomatic cerebral infarcts on brain magnetic resonance imaging[11]. These silent cerebral infarcts appear to be most closely related to the component of exaggerated morning BP surge associated with alpha-adrenergic activity[11].

ISOLATED NOCTURNAL HYPERTENSION

According to the latest ACC/AHA 2017 guidelines, nocturnal hypertension is defined as a BP more than 110/65 mm Hg at night[4]. Nocturnal hypertension and nocturnal dipping are separate entities; however, both of them are associated with increased risk of cardiovascular events[4]. Independently, nocturnal hypertension, even when not associated with nocturnal dip, has also been shown to have association with subclinical end organ damage, especially microalbuminuria[4]. Cerebrovascular bleeding, smoking and diabetes also correlate with nocturnal hypertension. Although female sex is more commonly associated with nocturnal dipping, the prevalence of nocturnal hypertension is found to be greater in the male population[4]. Isolated nocturnal hypertension upon ambulatory measurement as a novel clinical entity was first described by Li et al[41]. Isolated nocturnal hypertension predicts cardiovascular outcome in patients who are normotensive in the office or with ambulatory daytime BP measurement[41]. These patients generally

were recognised by the absence of BP decrease during night as compared to daytime BP[3]. Studies have shown that also normotensive subjects with a non-dipper BP profile have increased left ventricular mass and relative wall thickness, reduced myocardial diastolic function, increased urinary albumin excretion, increased prevalence of diabetic retinopathy, and impaired glucose tolerance[3]. This indicates that treatment based on the average of 24-h ABPM alone may not be enough[3]. Especially, when considering that elevated night-time BP is a better predictor than daytime BP in predicting fatal cardiovascular events and is related to high cardiovascular risk, independently of either clinic or daytime ABPM[3]. For this group, hypertension may also remain undiagnosed by self-BP measurement at home unless a self-measurement device with the possibility to measure BP at night would be used. However, if patients are already diagnosed with hypertension and receive anti-hypertensive treatment, night-time BP provides important information for optimising anti-hypertensive treatment. These patients might benefit from taking their drugs in the evening or having medication at both day and night-time[42]

MASKED HYPERTENSION

A cross-sectional study was conducted by Sobrino J, Domenech M, Camafort M et al in SPAIN in 2013, in normotensive healthcare workers aged at least 18 years with no known history of hypertension. The prevalence of MHT was 23.9%[43]. The most prevalent associated cardiovascular risk factors in the total population were smoking (24.9%), dyslipidemia (16.4%), a family history of premature cardiovascular disease (15.9%), and obesity (7.4%). A total of 45.4% of individuals had a family history of hypertension[44]. MHT was associated with male sex and prehypertension[45]. The study concluded that 24-h ambulatory BP monitoring should be routine in occupational health m checks in health workers, especially men and determining the prevalence of MHT in apparently healthy individuals may enable better risk stratification and management[46].

When a patient has a non-elevated BP reading in the office but elevated out-of-office BP reading, he/she is known to have masked hypertension (MH)[4]. Jackson Heart study[47], prevalence of MH on the basis of individual daytime, night time and 24-h readings was 22%, 41% and 26%, respectively, whereas overall

prevalence using all three combined was 44.1%[4]. Hence, all of them should be taken into consideration, but no single time period reading has been known to accurately calculate the prevalence[4]. These patients are at increased risk of organ damage, including renal dysfunction (proteinuria, decreased GFR), increased left ventricular index and hypertrophy, carotid atherosclerosis, stroke, myocardial infarction and increased level of urine albumin- to-creatinine ratio and serum cystatin C[4]. These patients should continue lifestyle modification and be started on antihypertensives. However, if the daytime ambulatory BP is not >130/80 mmHg, it is treated as elevated BP with lifestyle modification and annual ambulatory BP and/or home BP reading. Patients with masked hypertension have similar risks as those with hypertension, hence their treatment may lead to an overall reduction of cardiovascular events and thus in reduced burden for healthcare. In Banegas et al study, unlike most previous studies, it was observed to have greater mortality associated with masked hypertension than with sustained hypertension, which might be due to the delayed detection of masked hypertension in patients, who consequently could have more organ damage and cardiovascular disease than patients with sustained hypertension[7].

The prevalence of masked hypertension averages about 13% (range 10–17%) in population-based studies[8]. Several factors may raise out-of-office BP relative to office BP, such as younger age, male gender, smoking, alcohol consumption, physical activity, exercise-induced hypertension, anxiety, job stress, obesity, diabetes, CKD and family history of hypertension and the prevalence is higher when office BP is in the high normal range. Masked hypertension is frequently associated with other risk factors, asymptomatic organ damage and increased risk of diabetes and sustained hypertension. Meta-analyses of prospective studies indicate that the incidence of CV events is about two times higher than in true normotension and is similar to the incidence in sustained hypertension. The fact that masked hypertension is largely undetected and untreated may have contributed to this finding. In diabetic patients masked hypertension is associated with an increased risk of nephropathy, especially when the BP elevation occurs mainly during the night[8].

BP VARIABILITY

No matter which measurement device is used, blood pressure will always be a variable haemodynamic phenomenon that is influenced by many factors, which include the circumstances of measurement itself, emotion, exercise, meals, tobacco, alcohol, temperature, respiration, bladder distension, and pain; blood pressure is also influenced by age, race and diurnal variation, usually being lowest during sleep[10].

Short-term blood pressure variability is usually defined as the oscillation of blood pressure within 24 hours[48]. Fluctuation of blood pressure in a time range from minutes to hours mainly reflects the influence of central and autonomic modulation and the elastic properties of arteries[48]. In this way, the reduction of the ability of the arterial and cardiopulmonary reflexes to buffer changes in blood pressure due to behavioural or postural challenges and the alteration of arterial compliance can result in enhanced short-term BPV[48]. Expanding evidence has clearly demonstrated the influence of short-term and long-term BPV on target organ damage and cardiovascular events. For any given 24 h mean BP value, the prevalence and severity of target organ damage were linearly related to the extent of short-term BPV.

In another study, the prognostic relevance of short-term BPV was assessed in 73 hypertensive patients using intra-arterial BP measurement. After a follow-up period of 7 years, baseline BPV was found to be a contributor for the development of cardiovascular complications, particularly left ventricular hypertrophy. Daytime systolic BPV represents also a strong predictor of early carotid atherosclerosis progression in general population. In a 3-year follow-up study, progression of intima-media wall thickness was significantly greater in the patients with increased systolic BPV even after adjustment for other risk factors. Different studies have recently established the prognostic role of BPV for the development of arterial pathological changes. Another recent report proved the existence of differences between daytime and night time blood pressure variability regarding systemic atherosclerotic change and renal function. Using ABPM for assessment of BPV, meanwhile standard deviation of daytime systolic BPV, was strongly correlated

with renal vascular resistance; night time systolic BPV was significantly associated with intima-media thickness and plaque score. In addition to vascular damage, short-term BPV has been associated with left ventricular hypertrophy in normotensive Africans in the SABPA Study. Considering this association, the authors stress out that the assessment of short- term BPV could potentially add to the early detection of normotensive Africans at increased risk for the development of cardiovascular complications.

In addition, BPV also seems to contribute in the development of microvascular complications in type 1 and type 2 diabetes and with the progression of renal failure and mortality in patients at end-stage chronic kidney disease. Therefore, increased BPV is nowadays considered a new risk factor of cardiovascular disease and a possible new target for antihypertensive therapy. guidelines from the European Society of Hypertension (ESH) and the National Institute for Health Care and Excellence (NICE) acknowledge the importance of BPV in hypertension. The Task Force for the Management of Arterial Hypertension of the ESH and of the European Society of Cardiology (ESC) has recognized that the worsening of organ damage and the incidence of events are related to BPV assessed by the SD. In addition, the consensus recommends the use of long-acting drugs with more homogeneous BP lowering response over the 24 hours in order to minimize BPV[49]. The 2011 NICE Guideline for the Clinical Management of Primary Hypertension in Adults establishes the existence of new data showing differential effects of antihypertensive treatments on BPV, suggesting that excessive fluctuations in BP per se represent an independent predictor of clinical outcomes[48].

BLOOD PRESSURE PATTERNS RELATION TO AGE

In a post hoc analysis by Kaul et al (2018) reports trends in ambulatory blood pressure measurement (ABPM) with age in a large multicentre Indian all corners' population visiting primary care physicians[3]. ABPM data from 27 472 subjects (aged 51 ± 14 years, males 68.2%, treated 45.5%) were analysed and compared. Individual differences in ABPM patterns were compared for patients according to 10-year age categories. Results showed that systolic BP values started

to increase with age from the age of 40, BP variability (SD) increased from the age of 30 years. Diastolic BP values started to decrease from the age of 50 years. Masked Hypertension prevalence remained similar for all age-groups (range of 18.6% - 21.3%). The prevalence of reverse dippers increased with age from the youngest to oldest group with 7.3% - 34.2% ($P < .001$ for trend). Dippers prevalence decreased from 42.5% to 17.9% from the youngest to oldest age-groups, respectively ($P < .001$ for trend). These findings confirm that BP patterns show clear differences in trends with age, particularly regarding night time BP.

FAMILY HISTORY OF HYPERTENSION

A cross sectional observational study conducted by Sun et al in 2008 in healthy young subjects (aged 16 to 30 years), who were students of the Medical Centre of Peking University, attempted to determine whether there is a gradual increase in BP and an early change in arterial elasticity characteristics between young healthy individuals with or without a family history of hypertension and whether or not this increase is apparent in males as well as in females[50]. Sample consisted of 270 subjects, with 112 men and 158 women. They were divided into three groups according to the family history of hypertension: 1) subjects with at least one hypertensive parent (group A); 2) only hypertensive grandparents (group B); and 3) normotensive parents and grandparents (group C). The three groups. groups had an even distribution in age and education. Study concluded that, in a population of young subjects with no overt CV disease or symptoms at baseline, compared with normotensive offspring of normotensive parents, normotensive offspring of hypertensive parents have increased BP and impaired arterial properties, namely large and small arterial compliance as measured noninvasively by HDI. However, these differences were conspicuous only in men. It may be that alteration in arterial function is present already in young non-hypertensive subjects at risk for hypertension and may contribute to the progression to hypertension later in life.

GENETICS

A positive family history is a frequent feature in hypertensive patients, with the heritability estimated to vary between 35% and 50% in the majority of studies,

and heritability has been confirmed for ambulatory BP. Several rare, monogenic forms of hypertension have been described, such as glucocorticoid-remediable aldosteronism, Liddle's syndrome and others, where a single gene mutation fully explains the pathogenesis of hypertension and dictates the best treatment modality. Essential hypertension is a highly heterogeneous disorder with a multifactorial aetiology. Several genome-wide association studies and their meta-analyses point to a total of 29 single nucleotide polymorphisms, which are associated with systolic and/or diastolic BP. These findings might become useful contributors to risk scores for OD.

RELEVANCE

BP measurement is one of the most common non-invasive clinical practice tool to assess cardiovascular status of an individual & predict the likelihood of future cardiovascular events. ABPM provides a superior and more precise assessment of true BP than standard one-time office measurement.

In masked hypertensives the incidence of CV events is about two times higher than in true normotensives and is similar to the incidence in sustained hypertensive patients. The fact that masked hypertension is largely undetected and untreated may have contributed to this finding. In routine clinical practice, less attention is given to the nocturnal behaviour of blood pressure. ABPM also offers diagnostic insights into nocturnal patterns of blood pressure, such as dipping and non-dipping, reverse dipping, and excessive dipping, and the presence of nocturnal hypertension.

Although many researches have been done previously on the ABPM patterns in patients with hypertension, refractory hypertension, diabetes researches on currently healthy normotensive subjects are a few in India and no such study have been done so far in Kerala. This inadequacy necessitated us to conduct a study on the ABPM pattern in normotensive subjects in our population.

METHODOLOGY

STUDY DESIGN

Observational – cross sectional study

STUDY SUBJECTS

Normotensive staff & students (18 to 55 years of age) in Govt. Medical College, Kozhikode.

STUDY PERIOD

From January 1st 2019 to December 31st 2019

SAMPLE SIZE

100 normotensive subjects

Using the formula 4PQ/d2

P taken as 20.2% based on study published in US 2017 by Wang Y et.al using ABPM with precision of the study taken as 8.

INCLUSION CRITERIA

Healthy Normotensive subjects with no overt cardiovascular diseases, pre-existing comorbidities and normal on routine clinical examination.

Office BP normotensive criteria – SBP <120mmHg and DBP <80mmHg (JNC 8 & ACC/AHA 2017)

EXCLUSION CRITERIA

Patients not ready to give consent.

Pregnancy

Any known overt hepatic, renal, hematopoietic, respiratory & endocrine disorders.

History of cerebrovascular accidents, coronary artery disease, arrythmias, diabetes, anti-hypertensive treatment and use of any medications affecting cardiovascular system.

MATERIALS AND METHODS

Normotensive subjects meeting inclusion criteria and given the consent were included in the study. A detailed history, general and systemic examination, body mass index, routine blood investigations were done prior to inclusion in the study. Blood pressure was verified through 3 measurements with an a fully automated office BP machine (model MDD800) with patient in seated position on the right upper arm after a minimum rest period of 5 min. During the same visit the patient will be fitted with device for 24 hr ABPM. ABPM monitor used in the study were duly validated & calibrated according to British Hypertension Society (BHS) protocol and the standard set by the US Association for the Advancement of Medical Instrumentation (AAMI). ABPM Model used MEDITECH ABPM – 05 model.

Figure 5: ABPM machine

The patients were instructed to engage in normal activities and to refrain from strenuous exercise. It was also advised that at the time of cuff inflation, to stop moving and to keep the arm still with the cuff at heart level. Measurements are made at 15 min intervals during the day and every 30 min overnight. The measurements are downloaded to a computer and a range of analyses can be performed. At least 80% of BPs during daytime and night-time periods should be successful, if not the monitoring should be repeated.

ETHICAL ISSUES

A proper written consent was taken from the patients before participating in the study. They were given options to choose or to exempt from any point right from entering and throughout the period of study. Study was conducted using the ABPM device available in the department free of cost. IRC and IEC approval were obtained.

RESULTS

Data were analysed using IBM SPSS Statistics version 22 Interpreted using descriptive and inferential statistics. A total of 86 of the 100 subjects completed 24-h ABPM with enough successful readings (>80%) and were included for the analysis. Reason for excluding 14 subjects was because those subjects had <80% successful ABPM reading. Data of 86 healthy normotensive subjects were used for the research study analysis and the analysis was based on research objectives.

Organization of study findings

The data are presented under the following headings:

Section I: Distribution of samples according to different demographic and clinical variables.

Section II: Association of parameters of ambulatory blood pressure with selected demographic and clinical variables.

Section III: Correlation between nocturnal hypertension, Diurnal index, BMI and BP variability

SECTION I: DISTRIBUTION OF SAMPLES ACCORDING TO DIFFERENT DEMOGRAPHIC AND CLINICAL VARIABLES

This section deal with distribution of samples according to different demographic and clinical variables. The data were analyzed by using frequency and percentage distribution, range, mean, median, standard deviation, confidence interval and graphical representation.

Figure 6: Percentage distribution of samples according to age

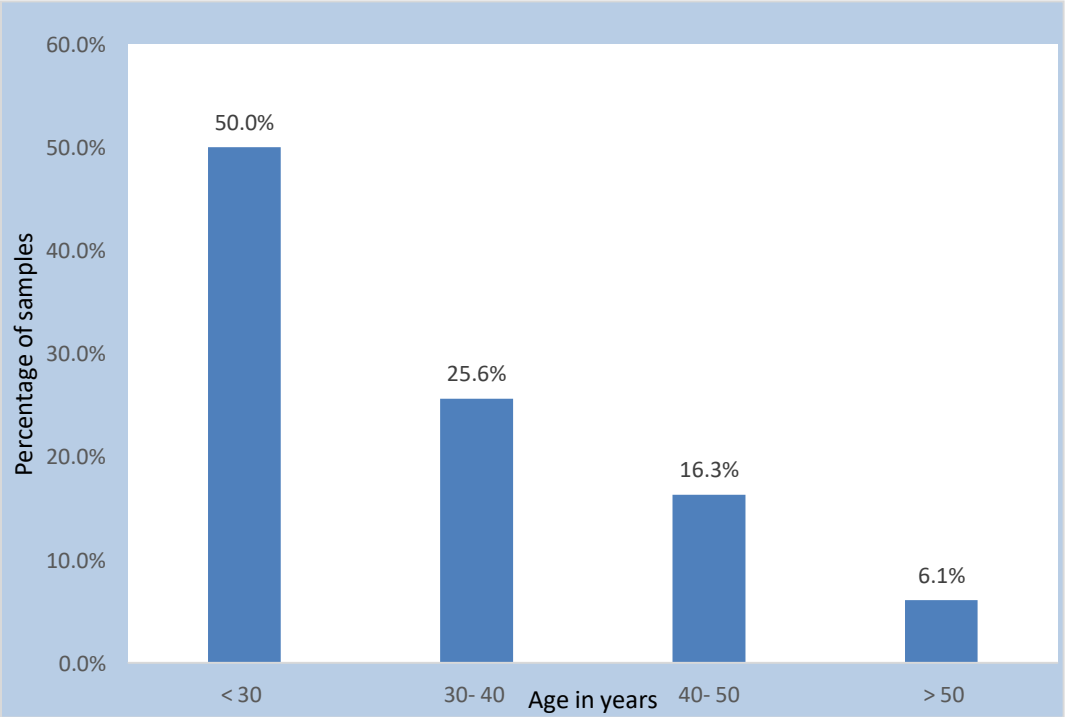
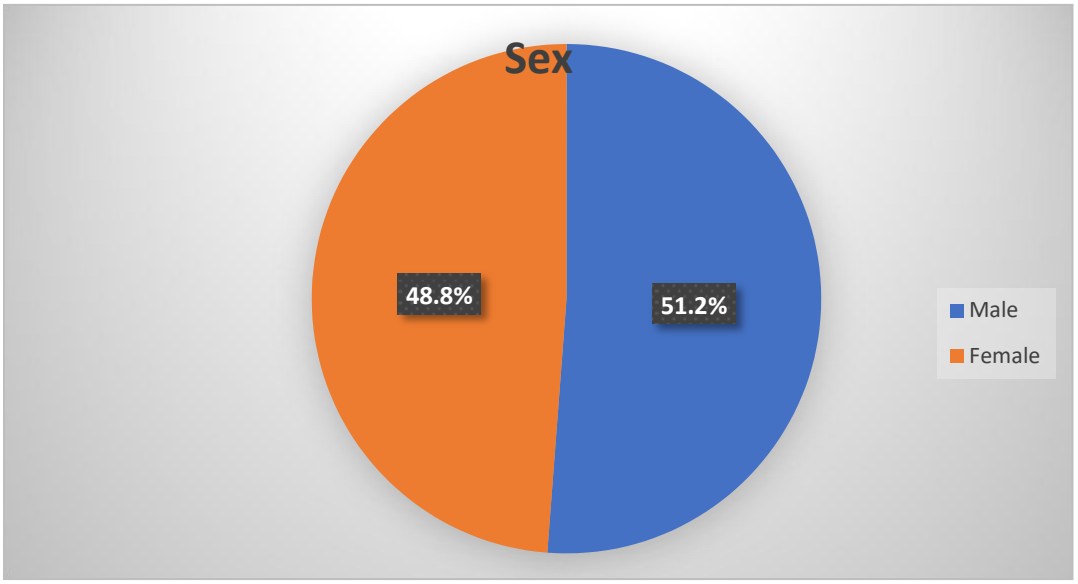


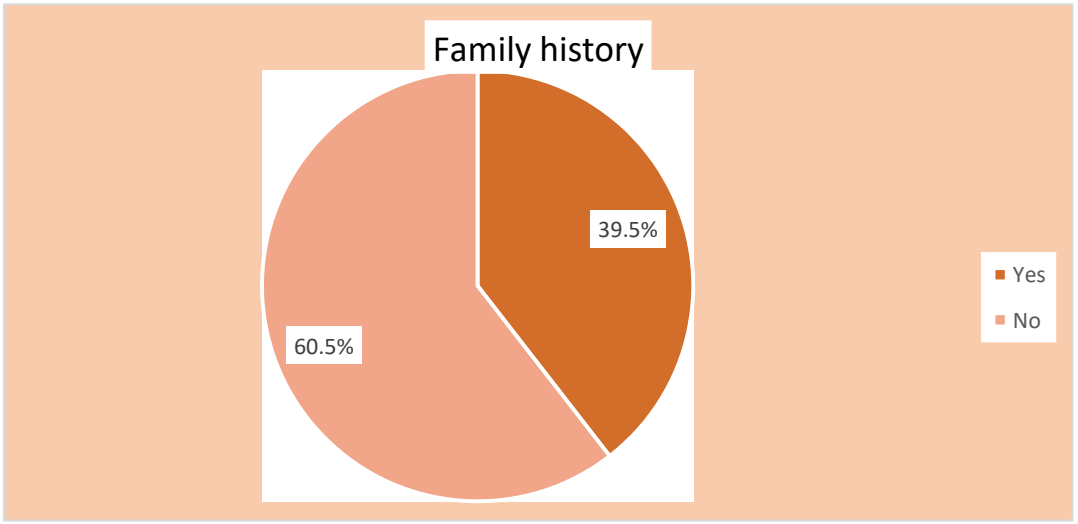
Diagram revealed that half of the samples 43 subjects out of 86 had age less than 30 years. Only 7 subjects (6.1%) had age above 50 years, 22 subjects (25.6%) belong to age group of 30-40 years and 14 subjects (16.3%) belong to age group 40- 50 years. The mean age obtained was 33.64 ± 9.44 and median was 30.50.

Figure 7: Percentage distribution of samples according to sex (N= 86)



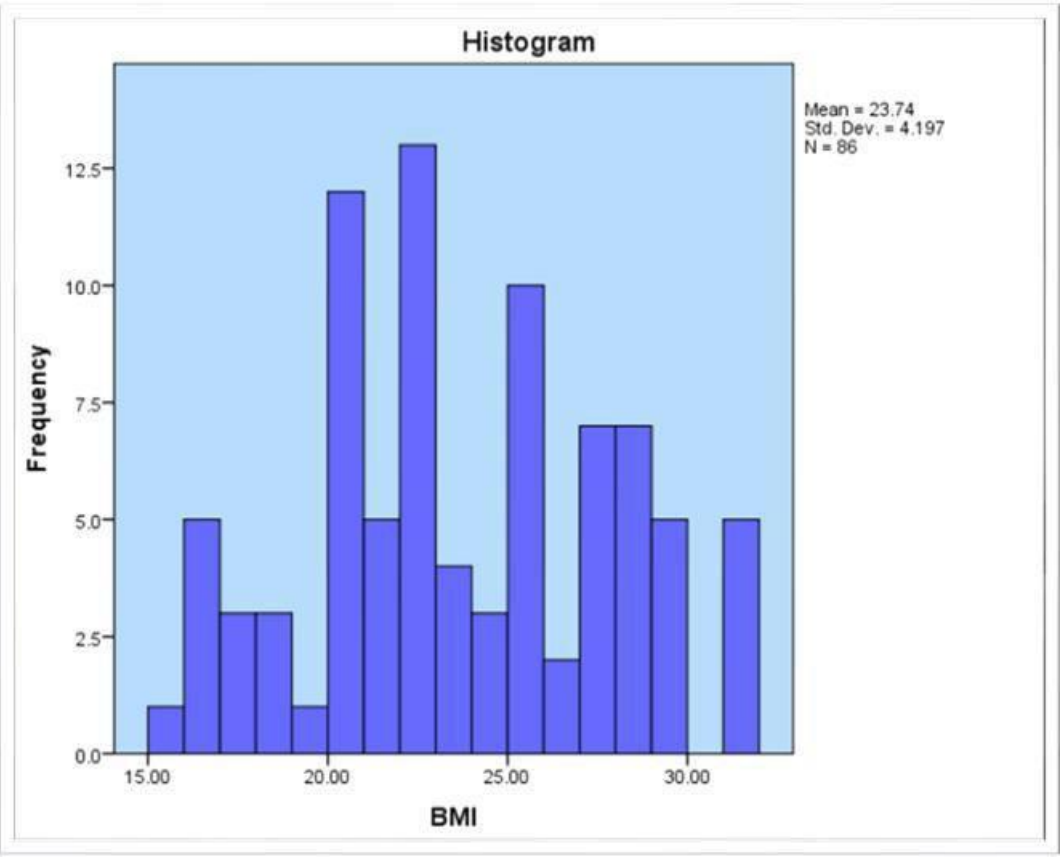
Out of 86 subjects included in analysis, highest percentage of samples (52.2%) were males and 42 (48.8%) were females.

Figure 8: Percentage distribution of samples according to family history



In this study, majority of samples (60.5%) did not have a family history of hypertension. Only 39.5 % had the family history of hypertension in the first degree relative.

Figure 9: Percentage distribution of samples according to Body Mass Index (N= 86)



Data shows that highest percentage of samples (38.4%) had normal BMI, followed by 36.0% having pre-obese. Only 5.0% fall in the category of obese. BMI classification used here was in accordance with the ASIAN criteria of BMI cut off.

Table 2: Prevalence of masked hypertension based on 24 hours ambulatory blood pressure (N=86)

Criteria	Frequency	Prevalence (in %)
< 130/ 80 mm Hg	78	9.30
≥ 130/ 80 mm Hg	8	

In this study the prevalence of masked hypertension was 9.30% based on 24hour ambulatory blood pressure monitoring.

Table 3: Prevalence if isolated nocturnal hypertension (N=86)

	N	Frequency of INH	Prevalence (%)
Males	42	1	2.38
Females	44	5	11.36
Total	86	6	6.98

Data shows that the prevalence of isolated nocturnal hypertension was 6.98%. The prevalence of isolated nocturnal hypertension among males was 2.38% and among females was 11.36%.

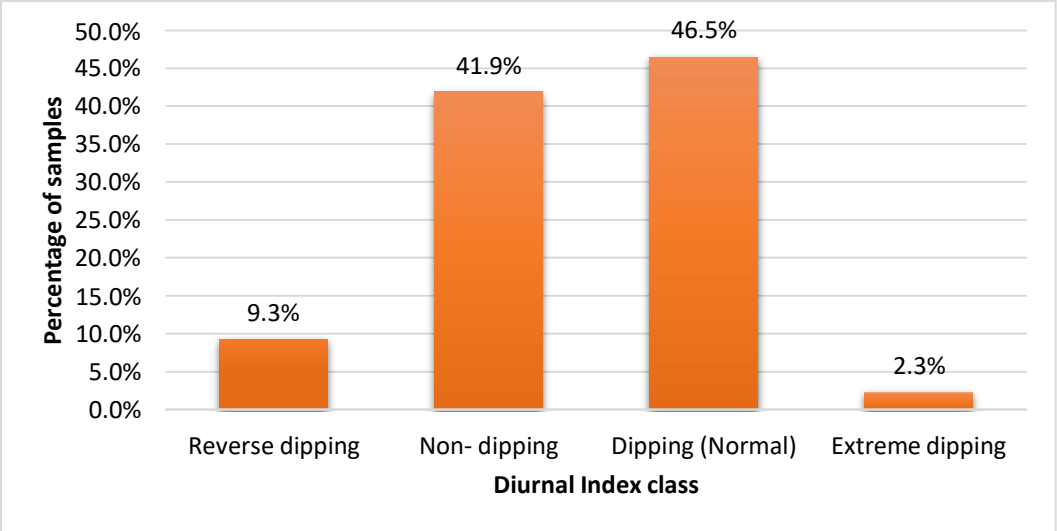
Table 4: Prevalence of BP variability (N=86)

	Criteria	Frequency	Prevalence (in %)
Normal	6 - 12 mm Hg	50	41.86
BP variability	> 12 mm Hg	36	

Data revealed that 36 out of 86 samples showed BP variability and hence the prevalence of BP variability was 41.86%.

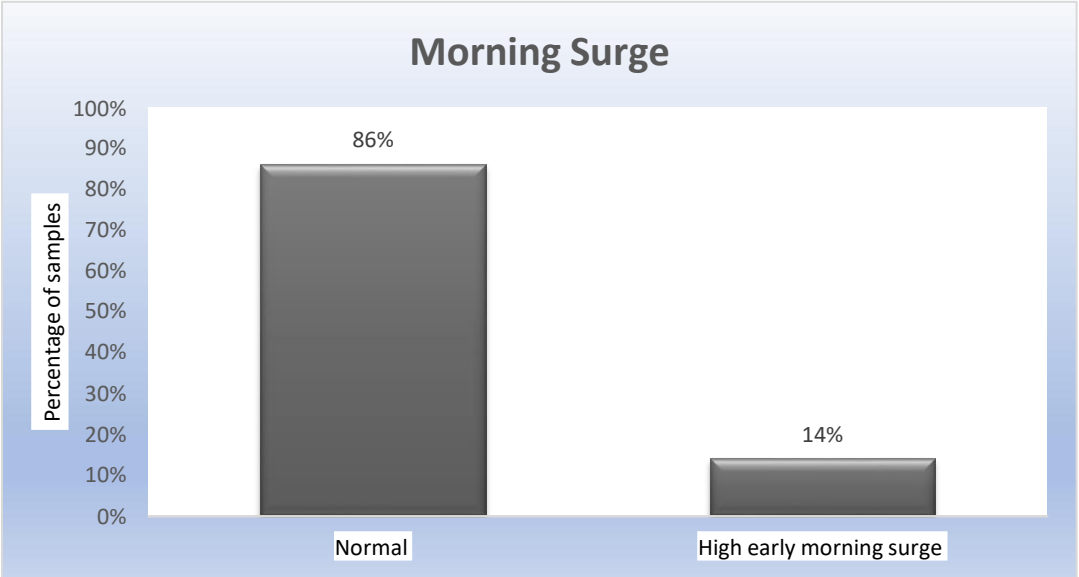
It is indicated in ABPM report as standard deviation.

Figure 10: Percentage distribution of samples based on Diurnal Index (DI)



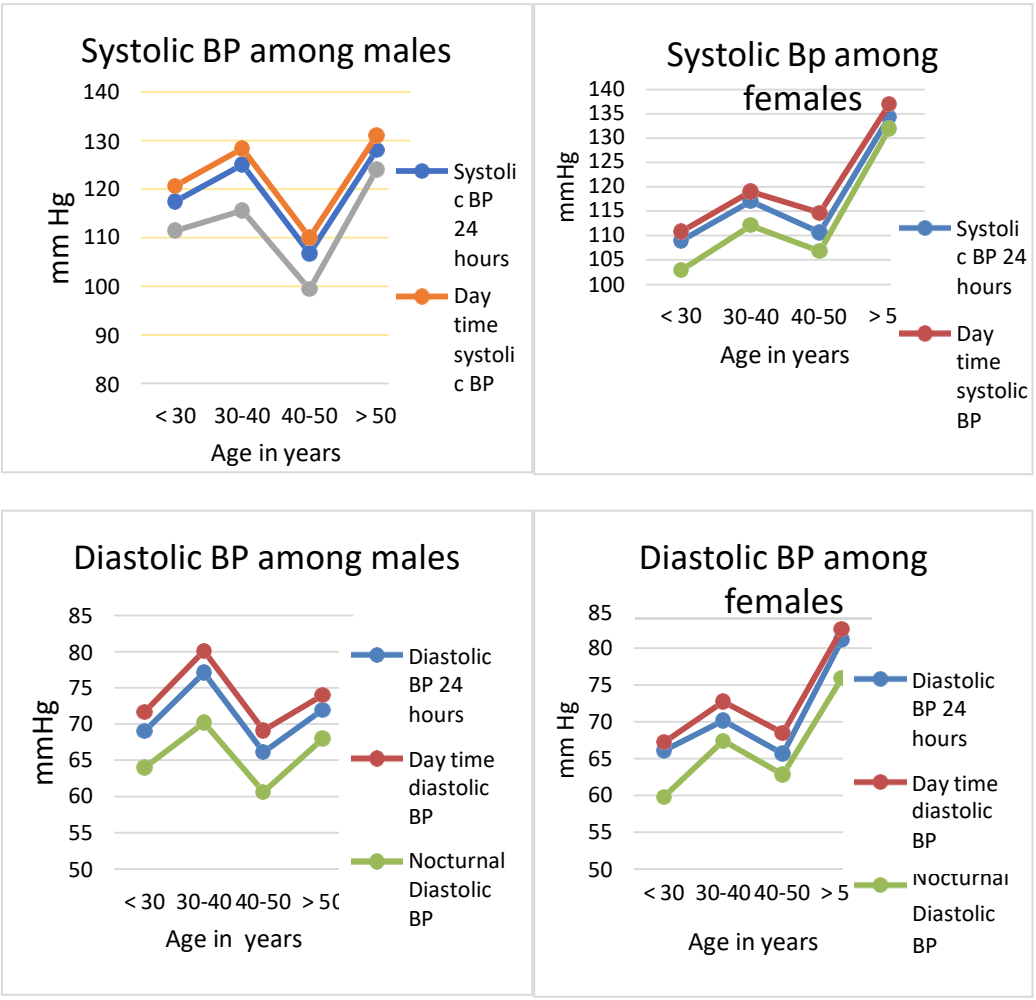
Based on diurnal index highest percentage of samples (46.5%) belong to the class of dipping (40 subjects out of 86), 36 subjects (41.9 %) had non- dipping, 8 subjects (9.3%) falls in the class of reverse dipping, and only 2 subjects (2.3%) belong to the class of extreme dipping.

Figure 11: Frequency and percentage distribution of samples according to morning surge



Data revealed that 12 out of 86 samples (14.0) had high early morning BP surge.

Figure 12: Line graph representing systolic and diastolic 24 hours, day time and night time BP among males and females according to age in years



Line graph shows that 24hour ambulatory systolic BP was higher in males compared to females in the age group < 30 years,30-40 years but was lower in males in the age group 40-50 years and >50 years when compared to females. For 24hour ambulatory diastolic BP, in the highest age group (>50 years) females shows higher value than males. Similar pattern is seen in day time systolic BP, diastolic BP and night time systolic BP and diastolic BP.

SECTION II: ASSOCIATION OF PARAMTERS OF AMBULATORY BLOOD PRESSURE WITH SELECTED DEMOGRAPHIC AND CLINICAL VARIABLES

This section deal with Association of parameters of ambulatory blood pressure with selected demographic and clinical variables. The data were analyzed by using Chi square test and Odds Ratio.

Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with age, sex, family history, BMI, day time BP and night time BP

Table 5: Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with age

Age (in years)	Normal BP (< 130/ 80 mm Hg)	Masked hypertension (≥ 130/ 80 mm Hg)	Prevalence of masked hypertension	χ^2 value	p value
< 30	41	2	4.7	10.523	0.015*
30- 40	20	2	9.1		
40- 50	13	1	7.1		
> 50	4	3	42.9		

Data revealed that the prevalence of masked hypertension were 4.7%, 9.1%, 7.1% and 42.9% for age groups below 30 years, 30- 40 years, 40- 50 years and above 50 years. Data also revealed that association of prevalence of masked hypertension with age. The χ^2 value obtained was 10.523 (p= 0.015), which was higher than the table value at 0.05 level of significance. Hence there was a significant association of prevalence of masked hypertension with age.

Table 6: Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with family history among males and females

Sex	Family history	Normal BP (< 130/ 80 mm Hg)	Masked hypertension (≥ 130/ 80 mm Hg)	Odds Ratio	χ^2 value	p value
Male	Yes	25	2	1.92	0.393	0.531**
	No	13	2			
Female	Yes	23	2	1.35	0.083	0.773**
	No	17	2			

Data revealed that the Odds Ratio was found to be 1.92 and 1.35 between masked hypertension and family history for males and females respectively. The data also revealed that the association of prevalence of masked hypertension with family history among males and females. The χ^2 value obtained was 0.393 ($p > 0.05$) and 0.083 ($p > 0.05$) for males and females respectively which was lower than the table value at 0.05 level of significance. Hence there was no significant association of prevalence of masked hypertension with family history among males and females.

Table 7: Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with family history

Family history	Normal BP (< 130/ 80 mm Hg)	Masked hypertension (≥ 130/ 80 mm Hg)	Odds ratio	χ^2 value	p value
Yes	30	4	0.63	0.404	0.525**
No	48	4			

Data revealed that the Odds ratio was found to be 0.63 between masked hypertension and family history. The data also revealed that the association of prevalence of masked hypertension with family history. The χ^2 value obtained was 0.404 ($p > 0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of prevalence of masked hypertension with family history.

Table 8: Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with BMI among males and females

Sex	BMI (kg/m^2)	Normal BP (< 130/ 80 mm Hg)	Masked hypertension (≥ 130/ 80 mm Hg)	χ^2 value	p value
Male	< 18.5	5	0	11.053	0.026*
	18.5 – 22.99	18	0		
	23.00- 24.99	3	0		
	25.00- 29.99	8	4		
	> 30	4	0		
Female	< 18.5	5	0	5.789	0.215**
	18.5 – 22.99	15	0		
	23.00- 24.99	4	0		
	25.00- 29.99	15	4		
	> 30	1	0		

Data revealed the association of prevalence of masked hypertension with Body Mass Index among males and females. The χ^2 value obtained was 11.053 (p= 0.026) for males which was higher than the table value at 0.05 level of significance. Hence there was a significant association of prevalence of masked hypertension with BMI among males. However the χ^2 value obtained was 5.789 (p> 0.05) for females which was lower than the table value at 0.05 level of significance. Hence there was no significant association of prevalence of masked hypertension with BMI among females.

Table 9: Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with Day time BP

Day time BP	Normal BP (< 130/ 80 mm Hg)	Masked hypertension (≥ 130/ 80 mm Hg)	χ^2 value	p value
< 135/ 85 mm Hg	78	2	62.888	<0.001*
≥ 135/ 85 mm Hg	0	6		

Data revealed that the association of prevalence of masked hypertension with day time BP. The χ^2 value obtained was 62.888 ($p< 0.001$) which was higher than the table value at 0.05 level of significance. Hence there was a significant association of prevalence of masked hypertension with day time BP.

Table 10: Association of prevalence of masked hypertension (based on 24 hours ambulatory BP) with nocturnal BP

Night time BP	Normal BP (< 130/ 80 mm Hg)	Masked hypertension (≥ 130/ 80 mm Hg)	χ^2 value	p value
< 120/ 70 mm Hg	73	0	49.531	0.001*
≥ 120/ 70 mm Hg	5	8		

Data revealed that the association of prevalence of masked hypertension with nocturnal BP. The χ^2 value obtained was 49.531 ($p< 0.001$) which was higher than the table value at 0.05 level of significance. Hence there was a significant association of prevalence of masked hypertension with nocturnal BP.

Association of prevalence of nocturnal BP with age, sex, family history and BMI

Table 11: Association of prevalence of night time BP with age

Age (in years)	Night time BP		χ^2 value	p value
	< 120/ 70 mm Hg	≥ 120/ 70 mm Hg		
< 30	41	2	22.657	<0.001*
30- 40	17	5		
40- 50	13	1		
> 50	2	5		

Data revealed that the association of prevalence of nocturnal BP with age. The χ^2 value obtained was 22.657 ($p< 0.001$) which was higher than the table value at 0.05 level of significance. Hence there was a significant association of prevalence of Nocturnal BP with age.

Table 12: Association of prevalence of nocturnal BP with sex

Sex	Nocturnal BP		Prevalence	Odds ratio	χ^2 value	p value
	Yes	No				
Male	8	36	22.2%	1.64	0.660	0.417**
Female	5	37	13.15%			

Data revealed that the Odds ratio was found to be 1.64 between nocturnal hypertension and sex. The prevalence of night time BP was 22.2% among males and 13.15 % among females. The χ^2 value obtained was 0.660 ($p> 0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of prevalence of nocturnal BP with sex.

Table 13: Association of prevalence of night time BP with family history

Family history	Night time BP		Odds ratio	χ^2 value	p value
	< 120/ 70 mm Hg	≥ 120/ 70 mm Hg			
Yes	28	6	0.73	0.281	0.596**
No	45	7			

Data revealed that the Odds ratio was found to be 0.73 between nocturnal hypertension and family history. The data also revealed the association of prevalence of nocturnal BP with family history. The χ^2 value obtained was 0.281 ($p > 0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of prevalence of nocturnal BP with family history.

Table 14: Association of prevalence of night time BP with BMI

BMI (kg/m^2)	Night time BP		χ^2 value	p value
	< 120/ 70 mm Hg	≥ 120/ 70 mm Hg		
< 18.5	10	0	16.296	0.003*
18.5 – 22.99	32	1		
23.00- 24.99	7	0		
25.00- 29.99	21	10		
> 30	3	2		

Data revealed that the association of prevalence of nocturnal BP with BMI. The χ^2 value obtained was 16.296 ($p = 0.003$) which was higher than the table value at 0.05 level of significance. Hence there was a significant association of prevalence of Nocturnal BP with BMI.

Association of diurnal index with age, sex, family history and BMI

Table 15: Association of Diurnal Index with age (N= 86)

Age (in years)	Diurnal index								χ^2 value	p value
	Reverse dipping		Non-dipping		Dipping (Normal)		Extreme dipping			
	f	Prevalence	f	Prevalence	f	Prevalence	f	Prevalence		
< 30	4	9.3	13	30.2	25	58.1	1	2.3	24.950	0.003*
30- 40	4	18.2	5	22.7	12	54.5	1	4.5		
40- 50	0	0.0	11	78.6	3	21.4	0	0.0		
> 50	0	0.0	7	100.0	0	0.0	0	0.0		

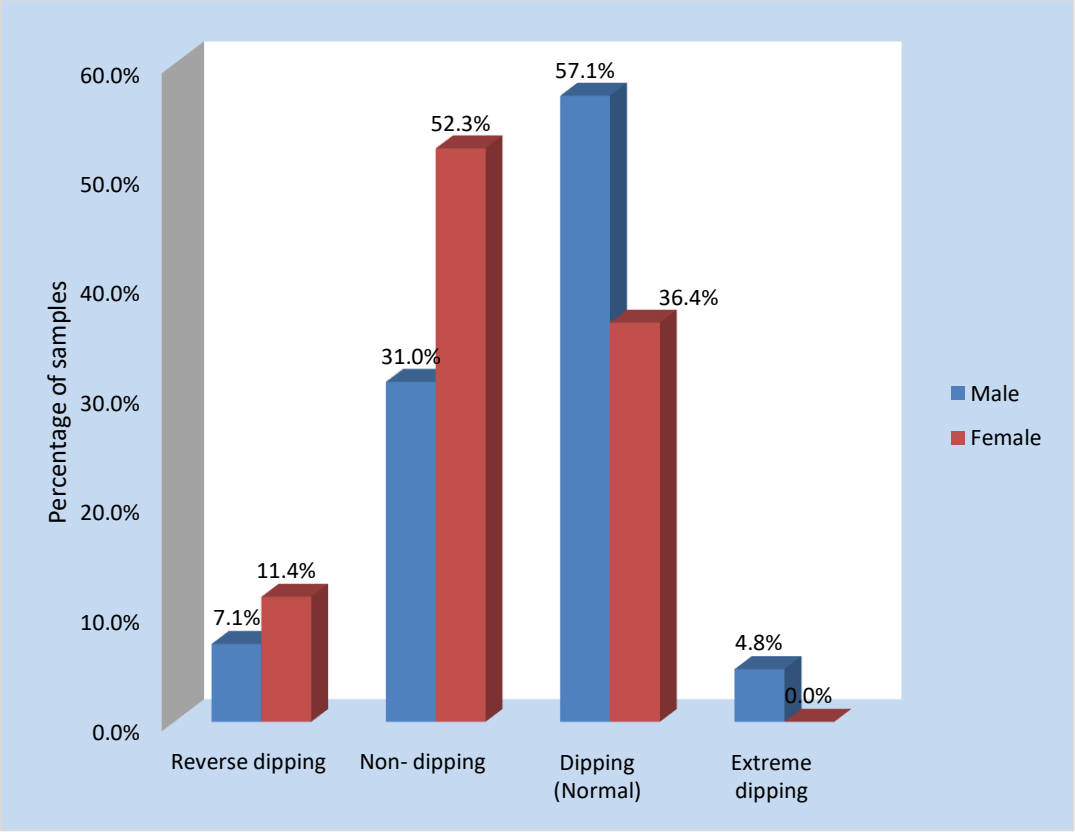
Data revealed that the prevalence of reverse dipping were 9.3% and 18.2% for age groups below 30 years and 30- 40 years. No samples had reverse dipping in the age group 30- 40 years and above 50 years. The prevalence of non-dipping was found to be 30.2 %, 22.7%, 78.6 % and 100.0% for age groups below 30 years, 30-40 years, 40- 50 years and above 50 years. The prevalence of dipping was 58.1%, 54.5 % and 21.4% for age groups below 30 years, 30- 40 years and 40-50 years. The prevalence of extreme dipping was 2.3 % and 4.5% for age groups below 30 years and 30- 40 years.

Data also revealed that the χ^2 value obtained was 24.950 ($p<0.05$) which was higher than the table value at 0.05 level of significance. Hence there a significant association of Diurnal Index with age.

Table 16: Association of Diurnal Index with sex (N= 86)

Sex	Diurnal index				χ^2 value	p value
	Reverse dipping	Non-dipping	Dipping (Normal)	Extreme dipping		
Male	3	13	24	2	6.835	0.077**
Female	5	23	16	0		

Figure 13: DI index with sex

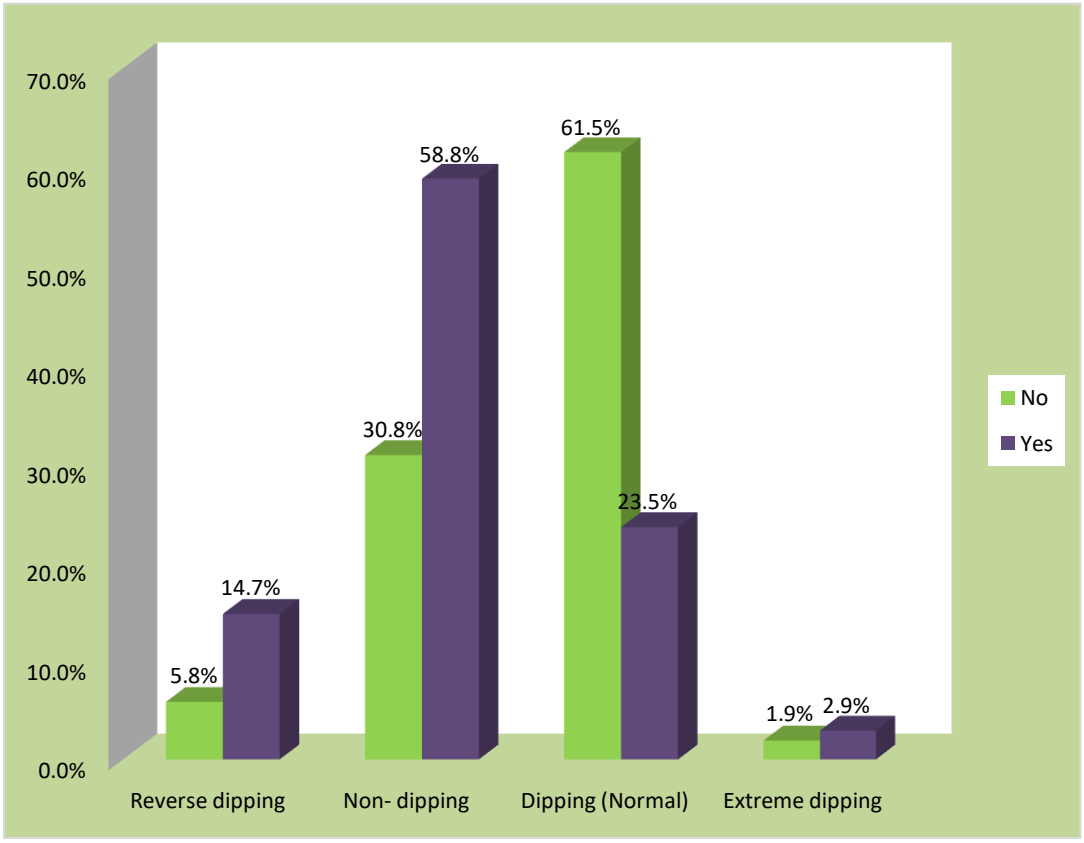


Data revealed that the association of Diurnal Index with sex. The χ^2 value obtained was 6.835 ($p>0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of Diurnal Index with sex.

Table 17: Association of Diurnal Index with family history (N= 86)

Family history	Diurnal index				χ^2 value	p value
	Reverse dipping	Non-dipping	Dipping (Normal)	Extreme dipping		
Yes	3	16	32	1	12.107	0.007*
No	5	20	8	1		

Figure 14: DI index with family history



Data revealed that the association of Diurnal Index with family history. The χ^2 value obtained was 12.107 ($p<0.05$) which was lower than the table value at 0.05 level of significance. Hence there was significant association of dipping, non-dipping, reverse dipping and extreme dipping pattern with family history.

Table 18: Association of Diurnal Index with BMI (N= 86)

BMI (kg/m^2)	Diurnal index				χ^2 value	p value
	Reverse dipping	Non-dipping	Dipping (Normal)	Extreme dipping		
< 18.5	0	6	4	0	15.372	0.222**
18.5 – 22.99	5	13	15	0		
23.00- 24.99	0	5	2	0		
25.00- 29.99	3	11	16	1		
> 30	0	1	3	1		

Data revealed that the association of Diurnal Index with BMI. The χ^2 value obtained was 15.372 ($p>0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of Diurnal Index with BMI.

Table 19: Association of prevalence of nocturnal BP with Diurnal Index (N= 86)

Diurnal index	Night time BP			χ^2 value	p value
	< 120/ 70 mm Hg	≥ 120/ 70 mm Hg	Prevalence		
Reverse dipping	7	1	12.5	1.138	0.768**
Non- dipping	29	7	19.4		
Dipping (Normal)	35	5	12.5		
Extreme dipping	2	0	0		

Data revealed that the prevalence of nocturnal BP were 12.5%, 19.4% and 12.5% in reverse dippers, no-dippers and dippers respectively. Data presented in table 1 revealed that the association of nocturnal BP with Diurnal Index. The χ^2 value obtained was 1.138 ($p>0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of nocturnal BP with Diurnal Index.

Table 20: Association of Non dipping and dipping BP with prevalence of masked hypertension (N= 86)

Masked hypertension	Non Dipping	Dipping	χ^2 value	p value
Yes	4	4	0.025	0.875
No	32	36		

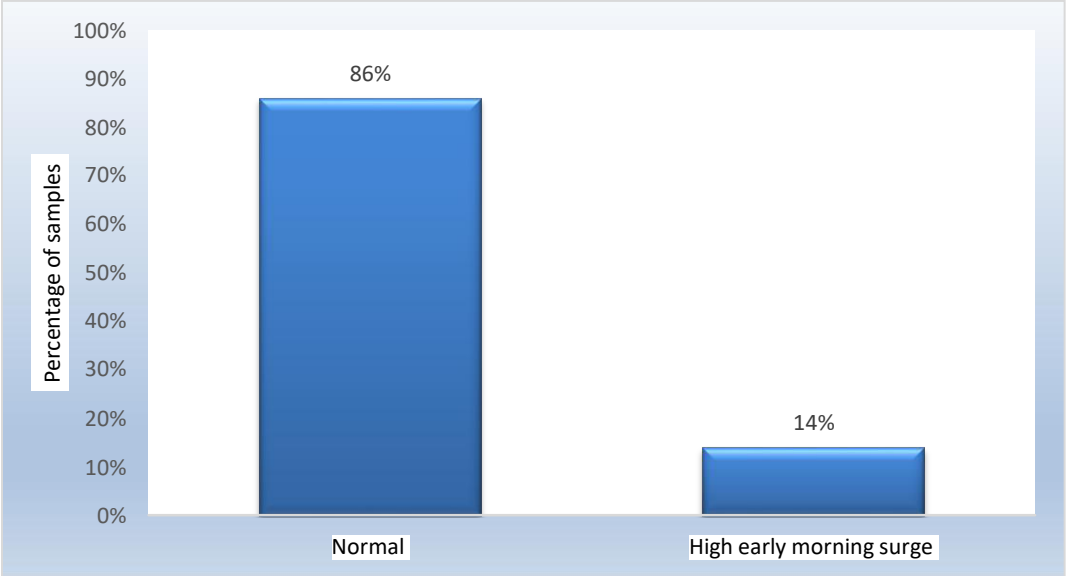
Data revealed that the association of non-dipping and dipping BP with prevalence of masked hypertension. The χ^2 value obtained was 0.025 ($p>0.05$) which was lower than the table value at 0.05 level of significance. Hence there was no significant association of non-dipping and dipping BP with prevalence of masked hypertension.

Table 21: Prevalence of BP variability (N=86)

	Criteria	Frequency	Prevalence (in %)
Normal	6 - 12 mm Hg	50	41.86
BP variability	> 12 mm Hg	36	

Data revealed that 36 out of 86 samples showed BP variability and hence the prevalence of BP variability was 41.86%.

Figure 15: Percentage distribution of samples according to morning surge



Data revealed that 12 out of 86 samples (14.0) had high early morning surge.

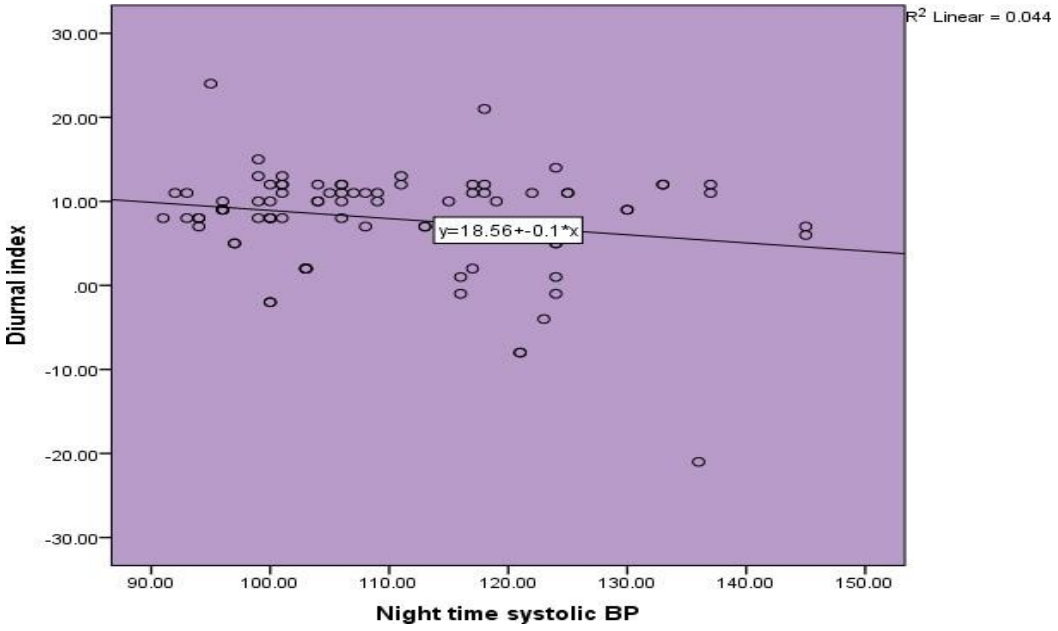
SECTION III: CORRELATION BETWEEN NOCTURNAL HYPERTENSION, DIURNAL INDEX, BMI AND BP VARIABILITY

This section deal with Correlation between nocturnal hypertension, Diurnal index, BMI and BP variability. The data were analyzed by using Karl Pearson's coefficient of correlation, and scatter diagram.

Table 22: Correlation between night time systolic BP and Diurnal Index (N=86)

	Mean ± SD	Coefficient of correlation (r)	Type of correlation	p value
Night time systolic BP	109.99 ± 13.26	-0.221	Low negative	0.049**
Diurnal index	7.95 ± 6.07			

Figure 16: Scatter diagram between night time systolic BP and Diurnal Index



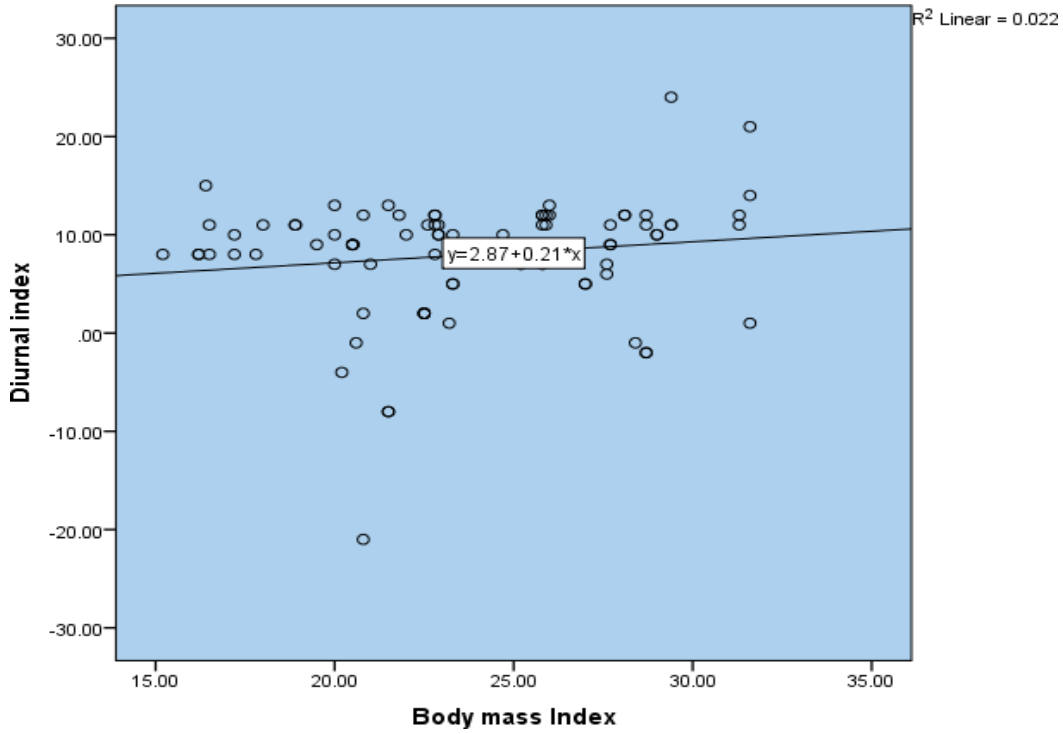
The data revealed that the Karl Pearson's coefficient of correlation, r value calculated was -0.211 indicating a low negative correlation between night time systolic BP and Diurnal Index. . The data also shows that there was significant correlation between night time systolic BP and Diurnal Index ($p>0.05$).

Table 23: Correlation between BMI and Diurnal Index (N=86)

	Mean ± SD	Coefficient of correlation (r)	Type of correlation	p value
BMI	23.74 ± 4.20	0.148	Low positive	0.174**
Diurnal index	7.95 ± 6.07			

** = Not significant

Figure 17: Scatter diagram between BMI and Diurnal Index



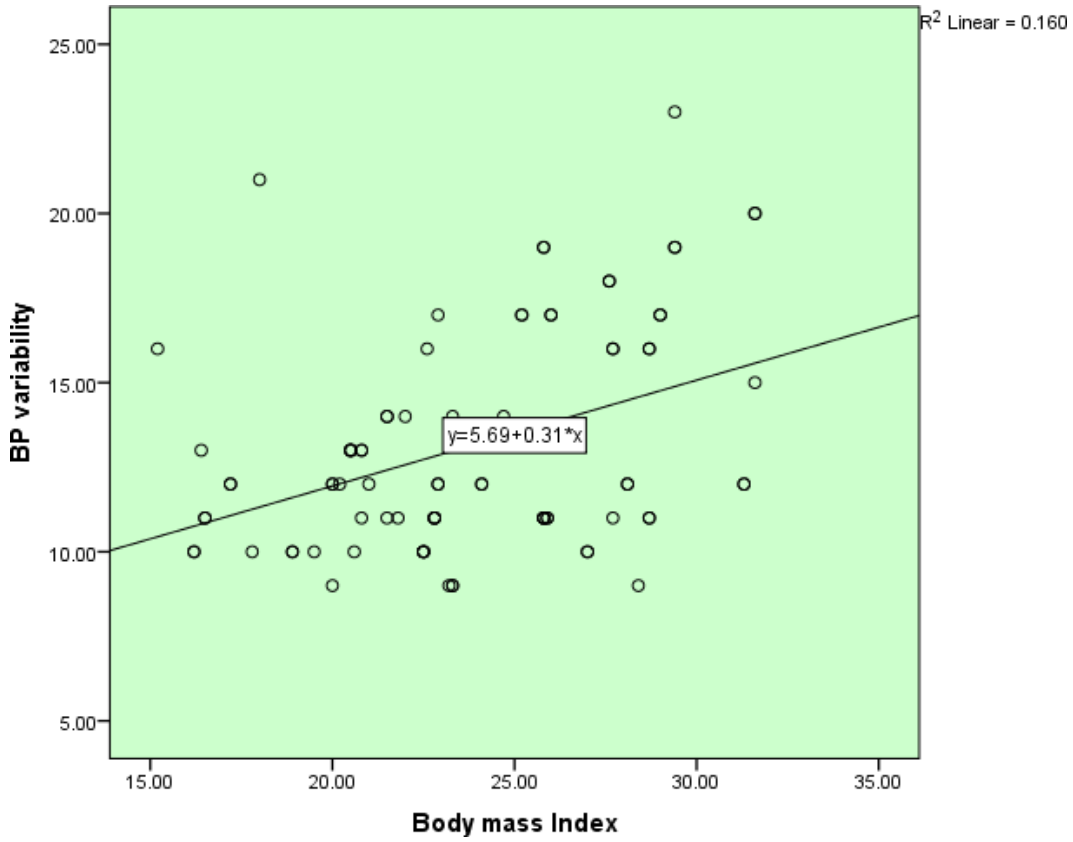
The data revealed that the Karl Pearson's coefficient of correlation, r value calculated was 0.148 indicating a low positive correlation between BMI and Diurnal Index. The data also shows that there was no significant correlation between night time systolic BP and Diurnal Index ($p > 0.05$).

Table 24: Correlation between BMI and BP variability

	Mean ± SD	Coefficient of correlation (r)	Type of correlation	p value
BMI	23.74 ± 4.20	0.401	Moderate positive	<0.001*
Standard deviation	13.12 ± 3.28			

* = significant at 0.05 level of significance

Figure 18: Scatter diagram between BMI and BP variability



The data revealed that the Karl Pearson's coefficient of correlation, r value calculated was 0.401 indicating a moderate positive correlation between BMI and BP variability. The data also shows that there was a significant correlation between BMI and BP variability (p <0.001).

DISCUSSION

ABPM provides a superior and more precise assessment of true BP than standard one-time measurement. One among the established benefit of ambulatory blood pressure monitoring is its utility to detect masked hypertension. In routine clinical practice, less attention is given to the nocturnal behaviour of blood pressure. ABPM also offers diagnostic insights into nocturnal patterns of blood pressure, such as dipping and non-dipping, reverse dipping, and excessive dipping, and the presence of nocturnal hypertension.

MASKED HYPERTENSION

When a patient has a non-elevated BP reading in the office but elevated out-of-office BP reading, he/she is known to have masked hypertension. And the defining criteria in the present study was 24hour mean ABPM systolic/diastolic BP $\geq$130/85 mm of Hg and whose office BP is in normotensive range. Prevalence of masked hypertension in this study was found to be 9.3%. It was associated with statistically significant association with age group from 4.7% to 42.9% from younger to older age and also with body mass index. But no significant association was found with sex and family history.

In a study conducted in Spain in 2013 by Sobrino J, Domenech M, Camafort M et al[51] in normotensive heath care workers the prevalence of masked hypertension was 23.9%. The study also revealed association of masked hypertension with obesity, male sex and a family history of premature cardiovascular disease.

ISOLATED NOCTURNAL HYPERTENSION

Elevated night-time BP is a better predictor than daytime BP in predicting adverse cardiovascular events and is associated with high cardiovascular risk, independently of either clinic or daytime ABPM. The defining criteria for isolated nocturnal hypertension in this study was blood pressure of systolic/diastolic BP $\geq$120/70 mm of Hg and a daytime blood pressure less than 135/85mmHg. The prevalence thus obtained was 6.98%. It was associated with a statistically significant association between age and body mass index and was more prevalent in males.

In a multi ethnic international database on ambulatory blood pressure monitoring, the prevalence of isolated nocturnal hypertension in Asians was 10.9% (Chinese) and 10.5% (Japanese)[52].

FAMILY HISTORY OF HYPERTENSION

Out of 86 subjects 8 were found to have masked hypertension based on 24hour ambulatory blood pressure monitoring and among them 4 subjects had family history of hypertension in the first degree relative and other 4 subjects did not have a positive family history. In this study a statistically significant association was not found between prevalence of masked hypertension and family history, but there was a significant association found between dipping, non-dipping, reverse dipping and extreme patterns with a positive family history.

But in a cross-sectional observational study conducted by Zhou L et al in 2008[50] in healthy young subjects (aged 16 to 30 years) Study concluded that, in a population of young subjects with no overt CV disease or symptoms at baseline, normotensive offspring of hypertensive parents have increased BP and impaired arterial properties, namely large and small arterial compliance as measured noninvasively by HDI and these differences were conspicuous only in men.

NOCTURNAL BLOOD PRESSURE PATTERNS

Night time blood pressure provides the most accurate representation of the BP phenotype in individual. ABPM is the method of choice for evaluation of night time BP.

With regard to the nocturnal dipping pattern, in the present study dippers constituted 46.5%, 41.9 % were non- dippers, 9.3% falls in the class of reverse dipping, and 2.3% were extreme dippers. Diurnal index was found to have significant association with age group & family history, but no statistically significant association was found between diurnal index and sex, body mass index and masked hypertension. There was significant correlation between night time blood pressure and diurnal index.

The findings of the study is similar to a study conducted by Vaidya N et al (2011)[25] on Circadian variability and nocturnal dipping pattern in blood pressure in

young normotensive subjects. The researchers found that Prevalence of extreme dipper, dipper and non-dipper was 13%, 63% and 24%, respectively.

The study findings also can be related to a study conducted by Friedman O et al (2009)[32] on Nocturnal blood pressure profiles among normotensive, controlled hypertensive and refractory hypertensive subjects. The investigators found that the proportion of non-dipping was 25.0% in normotensive samples.

The prevalence of reverse dippers increased from the youngest to older age group with 9.3% to 18.2%, whereas the dippers the opposite trend was seen, where the prevalence increased from 58.1% to 21.4% from the youngest to the oldest age groups. The prevalence of non-dippers increased with age group from 22.7% to 100%. For the prevalence of extreme Dippers, there was a small but significant increasing trend with age.

The findings of the study were comparable to a study conducted by Kaul U et al (2019)[3] on Blood pressure related to age: the India ABPM study, where the prevalence of reverse dippers increased with age from the youngest to oldest group with 7.3%-34.2%. Dippers prevalence decreased from 42.5% to 17.9% from the youngest to oldest age-groups.

BLOOD PRESSURE RELATED TO AGE AND SEX

Based on 24hour ambulatory systolic blood pressure it was found to be higher in males compared to females in the age group < 30 years,30-40 years but was lower in males in the age group 40-50 years and >50 years when compared to females. For 24hour ambulatory diastolic BP, in the highest age group (>50 years) females shows higher value than males. Similar pattern is seen in day time systolic BP, diastolic BP and night time systolic BP and diastolic BP.

The findings were contrary to the study conducted by Kaul et al[3] on the blood pressure related to age where daytime and nighttime SBP values increased with each age category and after the age of 30 years diastolic daytime BP started to decrease and continued with each age-group. Whereas the night time diastolic BP started from the age of 50 years.

BLOOD PRESSURE VARIABILITY

Studies has showed that increased BP variability is related to and leads to arterial damage, organ damage, impaired cognitive function, depression, and CKD. The prevalence of blood pressure variability in this study was found to be 41.86%. There was a significant correlation between BMI and BP variability.

CONCLUSION

- The present ABPM study in healthy normotensives shows that there is age-related differences in circadian BP patterns.
- Nighttime BP increased more with age so that there is higher prevalence of isolated nighttime hypertension with older age as compared to younger subjects.
- Prevalence of masked hypertension in present study is 9.3%.
- Masked hypertension has significant association with increasing age & BMI.
- Majority of the sample had nocturnal dipping pattern (46.5%) followed by non-dipping pattern (41.9%), highest percentage of non-dippers were in younger age group.
- Non dipping pattern showed significant association with family history.
- Body mass index has a positive correlation with BP variability & significant association with masked hypertension and nocturnal hypertension.

LIMITATIONS

- The findings of the study were limited to 86 subjects (data of 14 subjects were excluded for analysis)
- Subjects with <80% successful data, were not willing to repeat ABPM.
- Since the present study is a tertiary institutional based study, the prevalence values obtained may not reflect the community prevalence.
- Long term outcome and follow up was not available as it is a cross sectional study.

RECOMMENDATIONS

- A similar study can be conducted in a larger group of samples to draw more conclusive generalization.
- Proportionate sample (age, gender, family h/o) could been taken.
- Follow up study can be done in non-dippers, masked hypertensives.
- Case control study (with and without family history) can be conducted.

REFERENCES

1. Day WH. A global brief on Hypertension World Health Day 2013. Published online 2013.

2. Prabhakaran D, Jeemon P, Sharma M, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Heal. 2018; 6(12): e1339-e1351. doi:10.1016/S2214-109X(18)30407-8

3. Kaul U, Arambam P, Rao S, et al. Usefulness of ambulatory blood pressure measurement for hypertension management in India: the India ABPM study. J Hum Hypertens. 2020; 34(6): 457-467. doi:10.1038/s41371-019-0243-6

4. Dadlani A, Madan K, Sawhney JPS. Ambulatory blood pressure monitoring in clinical practice. Indian Heart J. 2019; 71(1): 91-97. doi:10.1016/j.ihj.2018.11.015

5. Pickering T. Ambulatory blood pressure monitoring: An historical perspective. Clin Cardiol. 1992;15(2 S):3-5. doi:10.1002/clc.4960151403

6. Unger T, Borghi C, Charchar F, et al. Clinical Practice Guidelines 2020 International Society of Hypertension Global Hypertension Practice Guidelines International Society of Hypertension. Published online 2020:1334-1357. doi:10.1161/ HYPERTENSIONAHA.120.15026

7. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. N Engl J Med. 2018;378(16):1509-1520. doi:10.1056/nejmoa1712231

8. Esc C, Cifkova R, Bo M, et al. 2013 ESH / ESC Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society. Published online 2013:2159-2219. doi:10.1093/eurheartj/eht151

9. Brien EO, Dolan E. Ambulatory Blood Pressure Monitoring for the Effective Management of Antihypertensive Drug Treatment. Clin Ther. 2016;38(10):2142-2151. doi:10.1016/j.clinthera.2016.08.006

10. O'Brien E, Asmar R, Beilin L, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. J Hypertens. 2005; 23(4): 697-701. doi:10.1097/01.hjh.0000163132.84890.c4

11. Kario K, Shin J, Chen CH, et al. Expert panel consensus recommendations for ambulatory blood pressure monitoring in Asia: The HOPE Asia Network. J Clin Hypertens. 2019;21(9):1250-1283. doi:10.1111/jch.13652

12. Kawano Y. Diurnal blood pressure variation and related behavioral factors. Hypertens Res. 2011;(December 2010):281-285. doi:10.1038/hr.2010.241

13. Takalo R, Korhonen I, Turjanmaa V, Majahalme S, Tuomisto M, Uusitalo A. Short-term Variability of Blood Pressure and Heart Rate in Borderline and Mildly Hypertensive Subjects. Hypertension 1994; 23(1):18-24.

14. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension. 2011; 57(1): 3-10. doi:10.1161/HYPERTENSIONAHA.109.133900

15. Peixoto AJ, White WB. Circadian blood pressure : Clinical implications based on the pathophysiology of its variability. Kidney Int. 2007;71(9):855-860. doi:10.1038/sj.ki.5002130

16. Grassi G, Bombelli M, Seravalle G, Oro RD, Quarti-trevano F. Diurnal blood pressure variation and sympathetic activity. 2010;(January):381-385. doi:10.1038/hr.2010.26

17. Elliott WJ. Circadian Variation in Blood Pressure: implications for the elderly patient. Am J Hypertens 1999;7061(98):43-49.

18. Iwahori T, Ueshima H, Torii S, et al. Diurnal variation of urinary sodium-to-potassium ratio in free-living Japanese individuals. Nat Publ Gr. 2017; (July 2016):658-664. doi:10.1038/hr.2016.187

19. Cuspidi C, Meani S, Salerno M, et al. Reproducibility of nocturnal blood pressure fall in early phases of untreated essential hypertension: A prospective observational study. J Hum Hypertens. 2004;18(7):503-509. doi:10.1038/sj.jhh.1001681

20. Lavie-nevo K, Pillar G. Evening – Morning Differences in Blood Pressure in Sleep Apnea Syndrome : Effect of Gender. Published online 2009:1064-1069. doi:10.1016/j.amjhyper.2006.02.018

21. Duggal A, Bal BS, Singh N. Study of Dipping and Non-Dipping Patterns in Patients of Type 2 Diabetes Mellitus with Hypertension and Its Association with Microalbuminuria 2017; (3): 20-24. doi:10.21276/aimdr.2017.3.2.ME6

22. O'Brien E. Dipping comes of age: The importance of nocturnal blood pressure. Hypertension. 2009; 53(3): 446-447. doi:10.1161/ HYPERTENSIONAHA.108.127571

23. Liu RQ, Qian Z, Trevathan E, et al. Poor sleep quality associated with high risk of hypertension and elevated blood pressure in China: Results from a large population-based study. Hypertens Res. 2016; 39(1): 54-59. doi:10.1038/hr.2015.98

24. Monahan M, Jowett S, Lovibond K, et al. Predicting out-of-office blood pressure in the clinic for the diagnosis of hypertension in primary care: An economic evaluation. Hypertension. 2018; 71(2): 250-261. doi:10.1161/HYPERTENSIONAHA.117.10244

25. Vaidya N, Pati AK, Parganiha A. Circadian variability and nocturnal dipping pattern in blood pressure in young normotensive subjects. Biol Rhythm Res. 2012;43(5):485-496. doi:10.1080/09291016.2011.605629

26. Normotensives C, Hoshide S, Kario K, Hoshide Y, Umeda Y, Hashimoto T. Associations Between Nondipping of Nocturnal Blood Pressure Decrease and Cardiovascular Target Organ Damage in Strictly Selected. Published online 2003:434-438. doi:10.1016/S0895-7061(03)00567-3

27. Bloomfield D, Park A. Night time blood pressure dip. World Journal of Cardiology. World J Cardiol. Jul 26, 2015; 7(7): 373-376. Published online doi:10.4330/wjc.v7.i7.373

28. Pasqualini R, Foroni M, Salvioli G, Mussi C. The "nondipper" elderly: A clinical entity or a bias? J Am Geriatr Soc. 2004;52:967–71.

29. Cuspidi C, Meani S, Salerno M, et al. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. J Hypertens. 2004;22:273–80.

30. Roman MJ, Pickering TG, Schwartz JE, Cavallini MC, Pini R, Devereux RB. Is the absence of a normal nocturnal fall in blood pressure (nondipping) associated with cardiovascular target organ damage ? J Hypertens 1997; 15(9): 968-78.

31. Lip GYH. Editorial Commentary.p.199-200. doi:10.1161/01.HYP. 0000049761.98155.7B

32. Friedman O, Logan AG. Nocturnal Blood Pressure Profiles among Normotensive, Controlled Hypertensive and Refractory Hypertensive Subjects. Can J Cardiol 2009; 25(9): e312-e316.

33. Tsioufis C, Andrikou I, Thomopoulos C, Syrseloudis D, Stergiou G, Stefanadis C. Increased nighttime blood pressure or nondipping profile for prediction of cardiovascular outcomes. J Hum Hypertens. Published online 2011:281-293. doi:10.1038/jhh.2010.113.

34. Yano Y, Kario K. Nocturnal blood pressure and cardiovascular disease : a review of recent advances. 2012;(December 2011):695-701. doi:10.1038/hr.2012.26

35. Viera AJ, Lin F, Hinderliter AL, Shimbo D, Person SD, Pletcher MJ et al. Nighttime Blood Pressure Dipping in Young Adults and Coronary Artery Calcium 10-15 Years Later: The Coronary Artery Risk Development in Young Adults Study. hypertension 2012; 59(6): 1157-63. Published online 2012. doi:10.1161/HYPERTENSIONAHA.112.191536

36. Elliott WJ. Circadian Variation in the Timing of Stroke Onset. Published online 1998:992-996.

37. Hoshide Y, Morinari M, Murata M, Kuroda T. Morning Surge in Blood Pressure as a Predictor of Silent and Clinical Cerebrovascular Disease in Elderly Hypertensives A Prospective Study. Published online 2003. doi:10.1161/01.CIR.0000056521.67546.AA

38. Grossman E. Ambulatory Blood Pressure Monitoring in the Diagnosis and Management of Hypertension. 2013;36:S307-S311. doi:10.2337/dcS13-2039

39. Bilo G, Grillo A, Guida V, Parati G. Morning blood pressure surge : pathophysiology, clinical relevance and therapeutic aspects. Published online 2018:47-56.

40. Kario K. Vascular damage in exaggerated morning surge in blood pressure. Editorial Commentary. Hypertension 2007; 49:771-772. doi:10.1161/01.HYP.0000259736.67231.18.

41. Xu T, Zhang Y, Tan X. Estimate of nocturnal blood pressure and detection of non-dippers based on clinical or ambulatory monitoring in the inpatient setting. BMC Cardiovasc Disord. 2013;13. doi:10.1186/1471-2261-13-37

42. Kaul U, Omboni S, Arambam P, et al. Blood pressure related to age: The India ABPM study. J Clin Hypertens. 2019;21(12):1784-1794. doi:10.1111/jch.13744

43. Tientcheu D, Ayers C, Das SR, McGuire DK, de Lemos JA, Khera A, et al. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: Analysis from the Dallas Heart Study. J Am Coll Cardiol. 2015;66(20):2159–69.

44. Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J, et al. Masked hypertension and elevated nighttime blood pressure in CKD: Prevalence and association with target organ damage. Clin J Am Soc Nephrol. 2016;11(4):642–52.

45. Blood I, Control P. Masked hypertension and cardiovascular outcomes : an updated systematic review and meta-analysis. Published online 2018:11-24.

46. Ha M. Metabolic risk factors and masked hypertension in the general population : the Finn-Home study. 2014;(November 2013):421-426. doi:10.1038/jhh.2013.129.

47. Booth JN 3rd, Diaz KM, Seals SR, Sims M, Ravenell J, Muntner P, et al. Masked hypertension and cardiovascular disease events in a prospective cohort of blacks: The Jackson Heart Study. Hypertension. 2016;68(2):501–10

48. Höcht C. Blood Pressure Variability : Prognostic Value and Therapeutic Implications. 2013; 2013: Article ID 398485.

49. Zhou TL, Kroon AA, Van Sloten TT, et al. Greater blood pressure variability is associated with lower cognitive performance: The Maastricht study. Hypertension. 2019; 73(4): 803-811. doi:10.1161/HYPERTENSIONAHA.118.12305

50. Zhou L, Chen Y, Sun N, Liu X. Family history of hypertension and arterial elasticity characteristics in healthy young people. Hypertens Res. 2008;31(5):833-839. doi:10.1291/hypres.31.833.

51. Sobrino J, Domenech M, Camafort M, Vinyoles E, Coca A, ESTHEN group investigators. Prevalence of masked hypertension and associated factors in normotensive healthcare workers. Blood Press Monit. 2013;18(6):326–31.

52. Li Y, Wang J-G. Isolated nocturnal hypertension: a disease masked in the dark: A disease masked in the dark. Hypertension. 2013;61(2):278–83.

ANNEXURES

PROFORMA

Case no:

Name: Age:

Sex: Occupation

BMI:

Family history of hypertension: YES/NO

Blood pressure in clinic:

General examination:

Systemic examination:

Sl. No	Age	Sex	F.H	Ht	Wt	BMI	Mean 24 SBP	Mean 24 DBP	Mean DAY SBP	Mean DAY DBP	Mean NYT SBP	Mean NYT DBP	DI	SD	PTE	HBI	Morning surge	MAP	Pulse
1	28	M	N	160	55	17.8	114	63	112	62	101	56	13	11	0	0	19	79	71
2	29	M	N	163	84	16.5	121	70	123	71	118	56	10	15	27	80	12	87	91
3	34	M	N	160	80	17.2	123	69	125	77	118	80	8	12	30	41	4	97	69
4	42	F	N	155	54	17.2	102	68	106	72	103	57	2	10	0	0	8	73	69
5	28	F	Y	166	58	16.5	110	68	116	73	108	61	10	12	6	10	16	83	71
6	30	M	N	170	80	18	114	63	112	62	108	60	3	11	4	1	9	80	61
7	27	M	N	175	63	15.2	114	70	118	74	116	69	-1	10	8	23	4	83	58
8	28	M	N	175	55	16.2	113	64	116	68	105	62	11	21	13	74	-1	84	72
9	28	M	Y	170	60	16.2	116	68	119	69	117	71	2	11	18	34	-11	88	81
10	27	F	Y	155	48	16.4	101	64	104	66	94	60	12	9	0	0	16	77	90
11	36	F	Y	156	69	20.2	123	75	123	77	124	69	-1	9	31	60	1	91	82
12	36	F	Y	151	55	20	110	64	112	66	100	59	13	12	3	2	21	81	89
13	28	M	n	173	74	18.9	127	77	131	82	119	67	10	14	38	88	11	94	74
14	27	M	Y	155	55	18.9	115	70	125	78	115	69	10	17	24	68	20	93	81
15	27	F	Y	170	63	20.8	104	67	109	70	100	60	8	11	2	5	8	79	80
16	35	M	Y	174	85	22.5	145	92	150	96	133	81	12	12	99	358	15	107	69
17	27	M	Y	178	52	22.5	109	67	114	71	99	58	15	13	1	1	27	82	74
18	28	M	N	167	80	22.5	145	92	150	96	137	84	9	11	87	377	27	110	65
19	26	F	N	162	76	20.5	112	68	114	71	104	53	10	17	9	27	34	77	76
20	31	M	N	167	64	20	112	68	114	71	109	61	5	12	9	17	10	83	57
21	25	M	Y	149	36	20.6	104	58	105	58	94	60	11	10	0	0	18	80	75
22	20	F	Y	152	45	21.5	102	68	106	72	96	61	11	10	2	4	19	79	80
23	40	F	N	155	62	22.9	112	60	116	63	106	66	8	11	2	1	13	80	71
24	39	M	Y	165	80	22.9	114	67	118	72	95	55	24	23	17	57	28	85	89
25	55	M	Y	172	80	22.8	128	72	131	74	124	68	5	10	36	69	9	91	63
26	53	F	N	150	62	22.8	140	84	145	86	145	74	4	18	73	372	11	101	54
27	34	F	Y	170	83	22.8	125	81	129	85	100	62	-2	16	32	88	12	81	73
28	26	F	N	170	75	22.8	118	71	118	74	111	64	11	17	12	38	40	84	81
29	24	F	N	151	43	20.5	104	58	105	58	92	60	12	10	9	16	10	84	60
30	23	F	N	165	45	20.5	101	60	102	60	93	61	11	11	0	0	18	76	71
31	23	F	N	155	48	20.5	101	60	102	60	99	53	11	12	2	6	2	75	84
32	38	F	N	155	50	22.5	120	67	118	68	136	87	-21	13	14	45	22	88	85
33	24	M	Y	170	60	19.5	109	67	114	71	104	61	8	13	8	11	18	81	74
34	41	M	N	148	50	21.5	107	66	110	70	101	62	8	11	4	6	11	80	73
35	37	F	N	158	79	20	125	76	125	77	124	74	1	20	44	145	3	92	82
36	50	F	Y	159	70	21.8	143	80	142	82	130	80	10	16	72	284	43	103	75
37	24	M	Y	182	75	22	132	78	138	83	122	69	11	16	56	153	4	96	74

Sl. No	Age	Sex	F.H	Ht	Wt	BMI	Mean 24 SBP	Mean 24 DBP	Mean DAY SBP	Mean DAY DBP	Mean NYT SBP	Mean NYT DBP	DI	SD	PTE	HBI	Morning surge	MAP	Pulse
38	18	F	N	146	38	21	97	57	99	59	91	52	8	10	5	7	11	80	80
39	33	F	Y	157	62	20.8	119	73	119	74	113	67	7	17	16	69	20	88	81
40	23	F	Y	155	56	22.6	102	68	104	60	97	60	12	9	0	0	0	74	76
41	28	M	N	169	84	22.9	134	71	139	76	125	63	11	19	65	211	-10	92	68
42	23	F	N	158	43	21.5	106	61	109	64	100	56	11	12	2	2	14	76	86
43	24	F	Y	160	39	20.8	108	68	112	79	99	63	12	16	8	26	11	81	87
44	45	F	N	156	50	24.7	107	66	110	70	96	60	9	13	8	11	10	82	72
45	27	F	Y	158	55	23.3	106	61	109	64	96	58	10	14	8	12	11	84	78
46	30	F	N	161	49	23.3	126	78	118	72	107	69	11	10	3	3	9	88	79
47	22	F	N	159	51	23.2	119	72	122	75	123	65	-4	12	24	56	7	85	87
48	27	F	Y	158	58	24.1	116	68	119	69	116	64	1	9	22	37	6	87	79
49	55	F	Y	150	58	24.1	125	76	125	77	120	76	7	19	32	137	34	96	77
50	36	F	N	169	74	23.3	119	72	122	75	117	67	5	11	20	19	4	87	67
51	25	F	Y	163	57	29	113	64	116	68	121	63	-8	14	17	48	9	80	74
52	30	M	N	172	69	26	113	64	116	68	106	59	10	14	9	34	10	80	72
53	44	F	N	155	54	29	100	60	107	62	103	57	2	10	0	0	8	73	69
54	48	F	N	155	62	26	112	60	116	63	106	66	8	11	2	1	13	80	71
55	26	M	N	155	48	25.9	100	64	103	65	99	53	12	12	2	6	2	75	84
56	51	F	Y	159	70	25.8	143	84	142	82	130	80	10	16	72	284	43	103	75
57	46	M	N	156	50	25.8	107	66	110	70	96	60	9	13	8	11	10	82	72
58	35	M	Y	174	85	25.8	**145**	88	151	92	133	81	12	12	99	358	15	107	69
59	26	F	N	162	76	25.8	110	63	115	57	104	53	10	17	9	27	34	77	76
60	52	F	N	150	62	27.6	140	84	145	86	145	74	8	18	73	372	11	101	54
61	55	M	Y	172	80	27.6	128	72	131	74	124	68	5	10	36	69	9	91	63
62	45	M	N	156	50	28.7	107	66	110	69	96	60	9	13	8	11	10	82	72
63	25	M	Y	149	36	29.4	104	58	105	58	94	60	11	10	0	0	18	80	75
64	31	M	N	167	64	29.4	115	68	115	67	109	61	5	12	9	17	10	83	57
65	27	M	Y	163	57	28.7	116	74	116	74	121	63	-8	14	17	48	9	80	74
66	53	F	Y	150	58	27.7	124	78	128	82	120	76	7	19	32	137	34	96	77
67	42	F	N	155	54	25.9	100	60	107	62	103	57	2	10	0	0	8	73	69
68	27	F	N	158	43	25.2	107	66	110	69	100	56	8	12	2	2	14	76	86
69	40	F	N	155	62	25.2	113	68	116	73	106	66	8	11	2	1	13	80	71
70	47	M	N	155	54	28.7	106	65	108	68	103	57	2	10	0	0	8	73	69
71	37	M	N	158	79	28.4	125	84	129	85	124	74	1	20	44	145	3	92	82
72	28	M	N	169	84	27.7	134	71	139	76	125	63	11	19	65	211	-10	92	68
73	44	M	N	148	50	27.7	107	66	110	70	101	62	8	11	4	6	11	80	73
74	23	M	Y	155	56	25.8	104	58	105	58	97	60	10	9	0	0	0	74	76

Sl. No	Age	Sex	F.H	Ht	Wt	BMI	Mean 24 SBP	Mean 24 DBP	Mean DAY SBP	Mean DAY DBP	Mean NYT SBP	Mean NYT DBP	DI	SD	PTE	HBI	Morning surge	MAP	Pulse
75	34	M	Y	170	83	25.8	125	84	129	85	100	62	-2	16	32	88	12	81	73
76	36	M	N	160	80	28.7	125	81	129	85	118	80	8	12	30	41	4	97	69
77	45	M	N	156	50	28.1	107	66	110	69	96	60	9	13	8	11	10	82	72
78	23	M	N	165	45	28.1	100	64	103	65	93	61	8	11	0	0	18	76	71
79	41	M	N	148	50	29.4	107	66	110	69	101	62	8	11	4	6	11	80	73
80	40	F	N	155	62	27	113	64	116	68	106	66	8	11	2	1	13	80	71
81	36	F	Y	151	55	27	110	67	112	69	100	59	13	12	3	2	21	81	89
82	26	F	N	170	75	31.6	126	78	118	72	111	64	11	17	12	38	40	84	81
83	33	F	Y	157	62	31.6	116	75	120	78	113	67	7	17	16	69	20	88	81
84	41	M	N	148	50	31.3	106	68	112	68	101	62	8	11	4	6	11	80	73
85	34	M	N	169	74	31.3	121	70	123	71	117	67	5	11	20	19	4	87	67
86	28	M	N	167	80	31.6	145	88	151	92	137	84	10	11	87	377	27	110	65

KEY TO MASTER CHART

Sex	M – Male F – Female
Family history of hypertension	N – No Y – Yes
Ht	Height
Wt	Weight
BMI	Body mass index
Mean 24 SBP	Mean 24hour systolic blood pressure
Mean 24 DBP	Mean 24hour diastolic blood pressure
Mean day SBP	Mean daytime systolic blood pressure
Mean day DBP	Mean daytime diastolic blood pressure
Mean NYT SBP	Mean night time systolic blood pressure
Mean NYT DBP	Mean night time diastolic blood pressure
DI	Diurnal/dipping index
SD	Standard deviation
PTE	Percent time elevation
HBI	Hyperbaric index
Morning surge	Early morning blood pressure surge
MAP	Mean arterial pressure of the subject
Pulse	Pulse rate of the subject

CONSENT IN ENGLISH

I have been informed by **Dr. SHILPA M MANUEL** about the nature of the study "**AMBULATORY BLOOD PRESSURE PATTERN IN HEALTHY NORMOTENSIVE SUBJECTS**" being conducted in the Department of General Medicine, Government Medical College, Kozhikode. Being aware of the implications of the study I consent to enroll myself in the study.

1. I have been informed that this study requires laboratory investigations and given my consent for the same.
2. I have been assured that my medical records will be kept confidential and no personal reference will be made in the study data.
3. I am also informed that by taking part in this study no cost of treatment shall be incurred by me.
4. I understand that my participation in this study is voluntary, I am free to refuse to participate and I am free to withdraw from the study at any time without any reason and that my refusal to participate or withdrawal of consent will not affect my treatment in any way.

I confirm that Dr. SHILPA M MANUEL has explained to me the purpose of research and the study procedure that I will undergo, in my own language. Therefore I agree to give consent to participate as a subject in this study.

Signature of the participant: Name :

Address :

Name of the Principal Investigator : Dr. SHILPA M MANUEL

Junior Resident

Dept. of General Medicine

Govt. Medical College, Kozhikode

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I am thankful to ***my family*** *who were constant source of encouragement throughout my life.*

Above all I thank ***God Almighty*** *for giving me the opportunity to undertake this work and the strength to complete it successfully.*

Dr. SHILPA M MANUEL

LIST OF ABBREVATIONS

ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
BPV	Blood pressure variability
CRP	C reactive protein
CV	Cardiovascular
DI	Diurnal or dipping index
HBI	Hyperbaric index
OBPM	Office blood pressure monitoring
OD	Organ damage
PTE	Percent time elevation
RAAS	Rennin angiotensin aldosterone system
WHO	World health organization