

The understanding of Hypertension has evolved over the last century. A single mercury manometer reading in the office as a target of normalization was considered the goal for the clinician attempting to prevent target organ damage. Oscillometric digital recording of BP has now made it possible to dispense with mercury which is toxic to the workers who manufacture manometers.

New digital instruments and self measuring devices have made it possible to do home and out of office BP measurements.<sup>1</sup> 24 hrs Ambulatory BP monitoring is now considered the Gold Standard in BP measurement and its usage has demonstrated that a single office reading is not enough.

BP variability: The patients of 24 hrs BP readings in ABPM are classified as

1. Normotensive
2. Sustained hypertension
3. White coat hypertension
4. Masked hypertension
5. Non Dippers
6. Night Risers Nocturnal hypertension
7. Early morning “spiker”
8. Hypotensive
9. Extreme dipper (standard deviation >20 mm seen in diseases like pheochromocytoma).

BP is recorded over 24 hrs during the “Awake” and “Sleep” period. Generally the Awake period is 6 a.m. to 10 p.m. (16 hours). The frequency of recording is generally set at every 20 minutes i.e. 3/hour. In the sleep period i.e., 10 p.m. to 6 a.m. The machine takes readings at 1-hourly intervals. These machine settings can be re-adjusted; for e.g., in a patient who works as a night watchman, the sleep setting may be reversed.

ABPM (ABPM) is a non-invasive method of obtaining blood pressure readings over a 24-hour period, whilst the patient is in his own environment, representing a true reflection of his blood pressure.

- It uses a small digital blood pressure recording machine that is attached to a belt around the body and which is connected to a cuff around the upper arm. It is small enough, so that patient can go about his normal daily life and even sleep wearing it.

- The machine then takes blood pressure readings at regular intervals throughout the day.
- At the end of the 24 hours, the patient can remove the machine and cuff and give it back to the hospital. The machine will have stored all the readings and these will then be analyzed for.
  1. 24 hour Average BP
  2. Daytime and nighttime BP pattern
  3. Nocturnal dipping status and excessive dipping if any
  4. Early morning surge
  5. BP load i.e. percentage of reading higher than normal
  6. BP variability derived from 95% confidence units (i.e.  $\pm 2$  SD) of readings

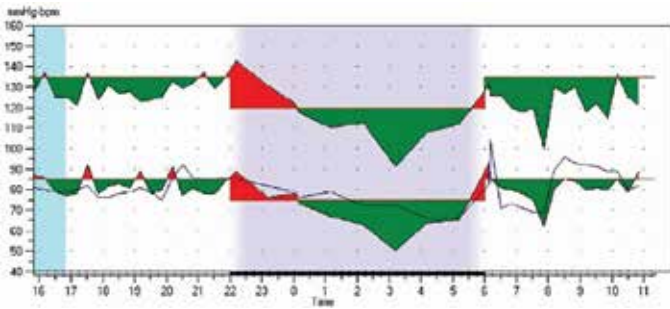
When should doctor order ABPM ?

- Use of ABPM to confirm diagnosis of Hypertension and initiate antihypertensive treatment following patients benefit most.
- Poorly controlled blood pressure (resistant or labile hypertension)
- Frequent hypotensive symptoms
- White coat hypertension (i.e. high BP in doctor’s clinic, normal at home )
- Masked hypertension (i.e. normal BP in doctor’s clinic, high at home)
- Nocturnal hypertension and early morning spike
- Fine adjustment of timing ,dose and type of antihypertensive medicine
- In “well controlled” or “prehypertensive” patients if there is a relentless progression of Target Organ Damage.

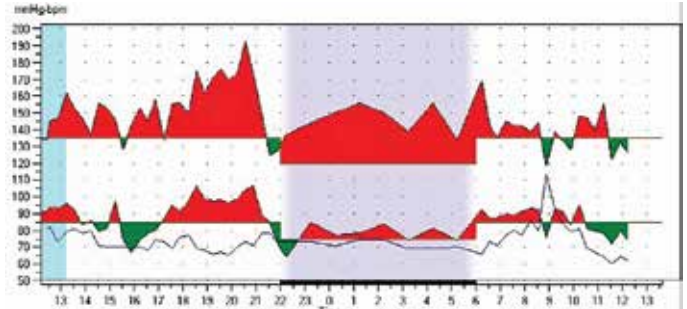
#### • A FEW CLASSICAL CHARTS OF ABPM (FIGURE 1 - FIGURE 7)

Please note:

- Light blue shaded area is white coat (1-1/2 hours after starting).
- Purple area, sleep time 10 p.m. to 6 a.m. (normal value 120/70)
- White area is wake period (normal value 135/85).
- Green denotes normalcy.

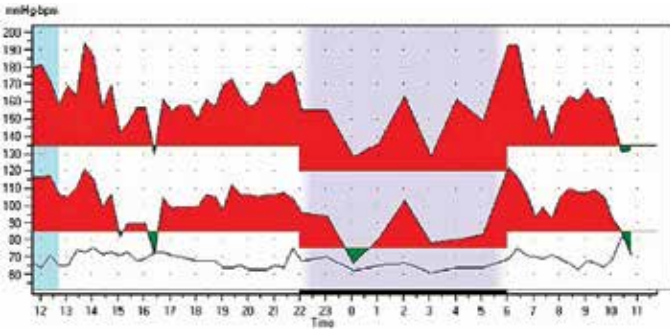


**Patient slept after midnight**  
**Fig. 1: Normal BP**

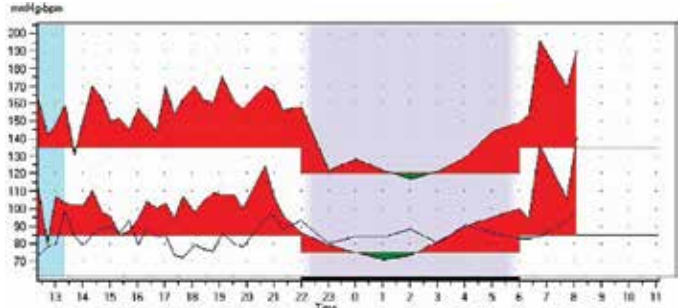


**Office Reading : 134/91 (start) 126/74 (end) 24 hr average reading at home : 147 / 86 Night average reading : 146 /77**

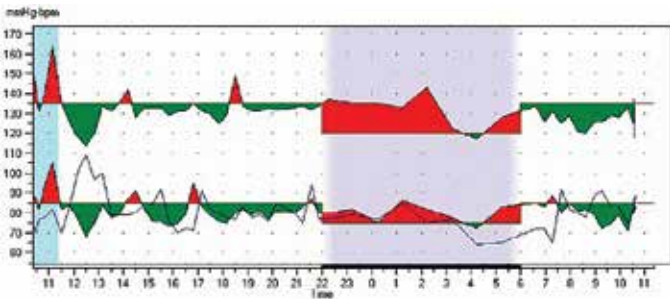
**Early Morning Surge**



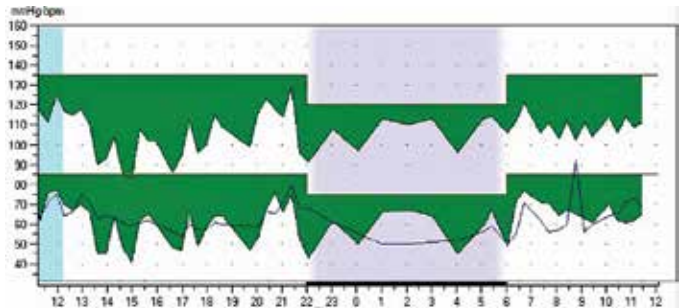
**24 hr Avg BP : 160 /100 ; Night Dip : 9.4 % sys,16 % diast**  
**Fig. 2: Sustained Hypertension**



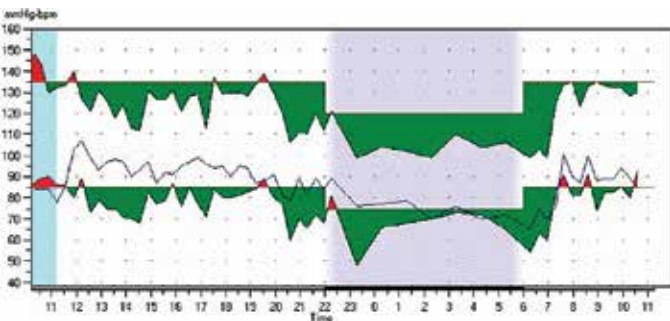
**Average Night reading: 130/81 Early morning reading: 190/110 6.43 am and 190/141 at 8 am**  
**Fig. 5: Masked Hypertension**



**Night Avg : 131 / 80 ; Day Avg : 131/82; % Dip : 0.1 %**  
**Fig. 3: Classical White Coat hypertension with non dipping**

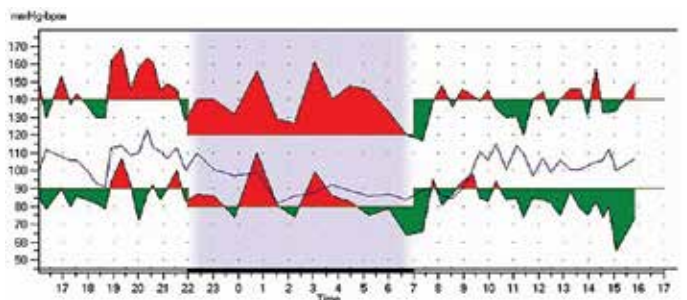


**Well controlled but patient experienced hypotensive symptoms on more than 3 occasions**  
**Fig. 6: Over-controlled hypertension**



**Office reading : 148/87 (start); 130 /93 (end); 24 hour average reading : 123 / 77; Daytime avg : 126/79 Night avg: 106/68**

**Fig. 4: Classical White Coat**



**Office BP and daytime BP well controlled, No nocturnal dip, Night average BP greater that awake BP**  
**Fig. 7: Classical Night Riser**

- Bright red denotes abnormalcy (high).

**WHITE COAT HYPERTENSION**

This phenomenon is often detected while investigating a patient who apparently has resistant hypertension. Many patients are already aware that they have white coat

hypertension. The incidence reported varies significantly between 2 to 5% of the normal population. This type of hypertension is first detected while doing ABPM. It is attributed to high-strung and emotionally labile people

692 who become nervous in the presence of their doctors or medical attendants. It is a benign phenomenon. This type of hypertension can mislead the physician into treating the patient over-aggressively and thereby causing significant symptoms attributable to the antihypertensive over-medication such as repeated fall, syncopal attacks, "micturition syncope" occurring particularly in old people at night, and even very rarely, fatality due to severe overtreatment of the patient. The incidence of subsequent development of hypertension is probably 15% more than the average normotensive population who do not have white coat hypertension. There are devices such as the Bp-TRU, (which I use in my department at BHIMS) and this instrument obviates in some patients, the use of ABPM for the detection of white coat hypertension. The Bp-TRU monitor is fixed on a wall in a quiet isolated room 4 feet x 4 feet with a chair on which the patient sits down. The attendant then takes a BP reading after 5 minutes with a standard manometer or an electronic oscillometric monitor. Thereafter, the correct size of BP cuff is put on the patient and the first reading of the Bp-TRU is taken in the presence of the attendant. The machine then is set to taking readings for another 5 times at any interval that it is adjustable. Usually, a 2-minute interval for each reading is kept so that the whole process takes about 10-12 minutes. During the last 5 readings, the patient is isolated and left alone in the quiet chamber which is well lit but has no extraneous sounds to disturb the patient and the average of the last 5 readings is taken. The average reading of the last 5 readings over 10 minutes interval is the Bp-TRU Avg reading. A large number of patients will have 5-10 mm drop between the first reading and the average of the last 5 readings. A similar protocol was adopted while doing

the blood pressure monitoring in the SPRINT trial. This is a very appropriate method of checking blood pressure but time-consuming and space-consuming. The device is made in Canada and costs about US\$1200 without custom duty if imported personally.

The limitations of Bp-TRU are that it should not be used if the attendant detects an arrhythmia during his initial reading.

**MASKED HYPERTENSION**

Masked Hypertension is the exact opposite of white coat hypertension, i.e., that is the blood pressure in the office is normal and the blood pressure at home is abnormal.

There are 3 types of Masked Hypertension.

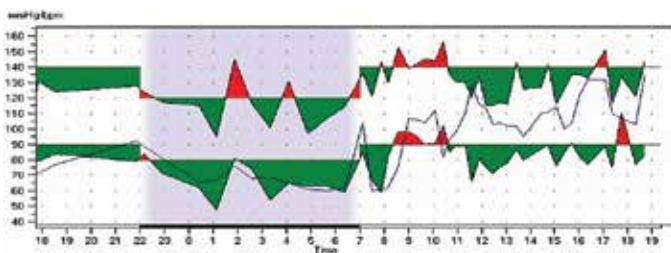
1. Daytime Hypertension, which is usually stress-induced.
2. Morning Hypertension or early morning spike of blood pressure.
3. Nocturnal hypertension.

Of these three, it is only possible to detect the one type of masked hypertension accurately, by the conventional home blood pressure monitoring and that is the stress-induced daytime hypertension.

In the past, good control of blood pressure was synonymous with good control of clinic blood pressure. Today, the triad of perfect BP control, which is aimed at reducing the incidence of target organ damage in patients with high blood pressure includes three major criteria.

1. Strict 24-hour average blood pressure below 130/80, and daytime average less than 135/85 using the ABPM data. (Note that this is equivalent to 140/90 using the mercury manometer). The average of night or sleep, i. e. readings between going to bed and waking up in the morning should be less than 120/70. The circadian rhythm should establish the presence of between 10 and 20 mm of nocturnal blood pressure dip during sleep and the BP variability should be less than that of the top 10 percentile of the BP. All 3 criteria must be met so as to avoid cardiovascular, cerebrovascular, and renal target organ damage.

Not all patients can undergo ABPM. Home blood



Well controlled on 3 drugs, but got up 2 times to pass urine at night.

Fig. 8: Well controlled hypertension

Modern Concept of Hypertension (Pickering has redefined hypertension)				
	Office BP (mmHg)	24-Hour ABPM Average (mmHg)	ABPM Daytime Average (mmHg)	ABPB Nighttime Average (mmHg)*
<b>True Normotensive</b>	Below 140/90	Below 130/80	Below 135/85	Below 120/70
<b>White Coat Hypertension</b>	Above 135/85	Below 130/80	Below 135/85	Below 120/70
<b>True Hypertensive</b>	Above 140/90	Above 130/80	Above 135/85	Above 120/70
<b>Masked Hypertension</b>	Below 135/85	Above 130/80	Above 135/85	Above 120/70

\*Night readings should be interpreted carefully since many patients may have fallacious readings due to ABPM machine interrupting the patient's sleep.

pressure monitoring is an important supplement. On a regular basis, home blood pressure is a good but limited substitute for those who cannot undergo ABPM and those who have already undergone ABPM and require further follow-up with home BP monitoring on a regular basis.

### MORNING BLOOD PRESSURE SURGE (MBPS)

It is well known that a large percentage of cardiovascular and cerebrovascular events of acute nature occur during the first five hours of the day, i.e. between 5 a.m. and 11 a.m. Muller et al<sup>2</sup> have shown that ischaemic strokes, sudden cardiac death and acute myocardial infarctions coincide with a rise of blood pressure between 5 and 11 a.m., and the incidence of these events is highest at that time. The rise of pressure during this time is known as the “morning surge of blood pressure” (MBPS). Part of this surge may occur before the waking period, followed by increase on waking up and further increase on standing up (also called orthostatic hypertension). There are various definitions and no one standard definition appears perfect. But, the conundrum of definitions culminates in the understanding that this is the most vulnerable period of blood pressure and any significant hemodynamic variation at this point in time affecting blood pressure and heart rate can be catastrophic. In particular, the difference between the sleep dip and the first 2 hours of the awake period contributes to this very vulnerable morning surge. Since the sleep blood pressure is most important in defining the surge, the home BP monitor is somewhat inadequate as it is currently developed. Therefore, one must presently depend on the ABPM for the sleep blood pressure. The Japanese are involved in developing new home nocturnal sleep time BP monitors with timers which unfortunately have not yet appeared in the Indian market. When they become available, they will be a useful boon for those who cannot undergo ABPM for various reasons.

MBPS is associated with left ventricular hypertrophy, left ventricular diastolic dysfunction, myocardial ischaemia and increased QTC and QTC dispersion. In diabetics, it is associated with albuminuria. In the presence of MBPS, it is found that there is higher CRP, higher IL-6, and higher IL-18.

Increase in inflammatory markers results in pathology of large arteries causing increase of carotid intima media thickness, development of vulnerable plaques, and increase in pulse wave velocity. In the smaller arteries, the media-to-lumen ratio of the resistant arteries increases and there is a high incidence of silent cerebral infarction. Additionally, there is increase of BP variability with high incidence of orthostatic hypertension and hypotension, and increase in the standard deviation of BP in the daytime to more than 15 mm. All the ambulatory machines record and exhibit the degree of standard deviation.

The patients with exaggerated MBPS exhibit increase of cardiac-afterload due to increase of arterial stiffness which leads to progressive left ventricular hypertrophy. The left ventricular hypertrophy is also manifested on echocardiography by left ventricular mass index and

the AE ratio, which represents diastolic dysfunction. Kaneda et al,<sup>3</sup> have reported that some well-controlled hypertensives with average BP full day less than 130/80 have significant LVMI, which is associated with sleep trough surge (MBPS). Even in normotensives who are not on treatment, the sleep trough surge of MBPS was significantly correlated with left ventricular mass index. Therefore, in untreated and in treated patients who are within the range of normal clinic BP, there is a population who will have a rise of MBPS leading to unexpected target organ damage.

As far as strokes are concerned, not only large infarcts occurring in the brain and producing clinically-obvious neurological damage are high in those who have MBPS, but also Silent Cerebral Infarcts (SCI) are a very strong surrogate marker of small strokes in patients who have early morning surge or exaggerated MBPS. The exaggeration of MBPS is related to increased alpha-adrenergic activity which can be blocked by the alpha-adrenergic agents like doxazosin.

### CHRONIC KIDNEY DISEASE

Chronic kidney disease, particularly in diabetics, has been shown to be very commonly presented with the absence of a dip or a non-dipping pattern of nocturnal hypertension. This non-dipping pattern usually precedes the onset of microalbuminuria, particularly in new-onset type II diabetic normotensive patients. The early morning surge under these circumstances is generally attributed to disrupted autoregulation of the afferent arterioles of the glomerulus. The Resistant Index using Doppler USG is an indicator of the degree of vascular resistance in the kidney and in disease states like diabetic kidney disease, an increased RI correlates with MBPS.

### WHAT CAUSES MBPS?

MBPS is closely associated with multiple factors which are age, essential hypertension, high-normal normotension i.e. pre-hypertensive state, diabetes, inflammation, excess alcohol intake, smoking, physical stress, psycho-emotional stress, and poor sleep quality. The positive factors are activation of neurohumoral systems such as the Renin Angiotensin System and the SNS. This may be related to the central and peripheral clock genes.

Another interesting finding is extreme dipping, i.e. when people dip more than 20 mm during sleep, they experience subsequently orthostatic hypotension, i.e. orthostatic increase in blood pressure and this steep increase in blood pressure can contribute to MBPS. Surge is also noted to be more on the first day of the week and in cold weather, particularly in old subjects. This may explain the higher incidence of cardiovascular events in winter in the cold countries and on the first morning of the week, i.e. Monday morning week.

### PATHOGENESIS OF EARLY MORNING SURGE OR MBPS

The neurohumoral factors in the body exhibit a circadian rhythm. The levels of plasma norepinephrine rise between 4 a.m. and 10 a.m. Similarly, the Renin Angiotensin System has a surge during the same period. An exaggeration of

694 this surge related to sympathetic nervous system over-activity is the cause of MBPS. An increase for hemostatic abnormalities with thrombotic over-activity during the early morning surge is also noted. These are manifested as hypercoagulability, low fibrinolytic activity, i.e., increase in the PAI-1 (Plasminogen Activator Inhibitor 1) and increase in platelet aggregation. The JMS ABPM study ( ) showed an increase of stroke risk in patients with MBPS was associated with increased plasma levels of Prothrombin Factor 1 + 2 (F1+2). The F1+2 is a biomarker of activated coagulation factor X-A and PAI-1 is known to inhibit fibrinolysis. There are vascular factors which lead to big-vessel stiffness and remodeling of small blood vessels with increase in media thickness and narrowing of the lumen diameter resulting in increase of Media/Lumen (M/L) ratio, which is a measure of remodeling of the subcutaneous arteries in patients with essential hypertension such as radial, femoral, etc.

Morning blood pressure rise and Sustained nocturnal hypertension are very similar in causing increased target organ damage. Nocturnal blood pressure is of two types; non-dipping and rising. In considering the definition of nocturnal hypertension, we are considering the period between falling asleep and waking up totally. The risks involved in nocturnal hypertension are increased cardiovascular and stroke risks. A study by Komori in 2008<sup>4</sup> has shown a significantly poorer stroke-free survival in patients whose mean sleep systolic BP is above 120 mmHg.

It is impossible to enumerate all the variables of ambulatory blood pressure; however, in conclusion, one may say that the order of today is to subject every difficult-to-treat hypertension with one round of ABPM.

### BLOOD PRESSURE VARIABILITY

The understanding of blood pressure variability and the presence of this enigmatic phenomenon, which has been discovered only due to the availability of ABPM has led to definition of a new syndrome called SHATS (Systemic Hemodynamic Atherothrombotic Syndrome).<sup>1</sup>

### THE PATHOGENIC MECHANISMS INVOLVED IN DEVELOPMENT OF SHATS

The following risk factors contribute to target organ damage in the brain, heart, kidneys, and the arteries including the aorta, i.e.,

- Diabetes.
- Dyslipidemia.
- Inflammation.
- Thrombogenesis.
- CKD.

The target organ damage produces neurohumoral activation thereby involving both; the SNS in the brain, and increasing the central aortic blood pressure. In the brain, sympathetic activation produces baroreceptor

insensitivity. Due to increased central aortic pressure, the large arteries become stiff. The smaller arteries are remodeled due to endothelial damage and become narrowed. Together, these two events produce reduced attenuation of pulse wave, increased blood pressure variability, and reduced autoregulation. These cause overall pulsatile hemodynamic stress which further accentuates target organ damage.

### CLINICAL MANIFESTATIONS OF PRESSURE VARIABILITY

- A. High peak pressures due to:
- Orthostatic hypertension (Blood pressure rises immediately on standing up).
  - MBPS (morning blood pressure surge).
  - Daytime blood pressure surge.
  - Absence of nocturnal dip.
  - Nocturnal rise in pressure (nocturnal hypertension).
- B. Low pressure dips
- Orthostatic hypotension
  - Extreme dipper (more than 20 mm at night)

Such patients have worsening of target organ damage in a vicious cycle manner because the initial pathogenesis is due to already existing target organ damage.

In conclusion, not all hypertensives are easily identifiable by office BP, masked hypertensive, early morning “spikers”, Nocturnal “Risers”, pre hypertensives with other risk factors, are invisible hypertensives at high risk of TOD. Also, white coat hypertensives are at risk of suffering from over-aggressive reduction of blood pressure.

The following individuals should be subjected to ABPM:

- Every new case of elevated office blood pressure.
- Prehypertensive patients with predictors of masked hypertension such as CKD, DM, PCOS, OSA.
- Those patients who have apparent good control of office BP, but persistent progression of target organ damage.
- Resistant hypertension not on goal on 3 medications or controlled using 4 medications.

### REFERENCES

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