Contributions of Ambulatory Blood Pressure Monitoring in Prognostic Stratification of Hypertensive Patient

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Modern medicine emphasizes the concept of homeostasis "constancy of the intern milieu".

Accordingly, it is assumed that biological functions are relatively stable during 24 h and other times periods, and that the exacerbation of disease and risk of several clinical events are of equal probability each hour of the day and night, day of month, and month of year [1].

Today, modern laboratory methods require frequently devices for ambulatory monitoring in order to measure different variables, such as, blood pressure (BP), heart rate, and brain activity, continuously throughout the 24 h. This is necessary because of the physiological and pathological alterations of the biological rhythms.

Most practicioners know very little about biological rhythms [1].

The blood pressure values, a heart rate of 72 beats/min results in 103680 pulse waves in 24 h, with the same variations of blood pressure [2].

Because of this, in the 60’s Sokolow and Perloff [3] introduced the ambulatory blood pressure monitoring (ABPM), establishing in 1983 its clinical utility. Early, the method was utilized in investigation trials, but now it is more and more used in the clinical practice, because it gives additional information to office and home measurements.

The ABPM is a significative contribution in the diagnostic, prognostic, and therapeutic evaluation of BP and its reproducibility is better than the office measurements both short and large time periods.

A number of studies showed that ABPM is better than office measurements for diagnostic and evaluation of hypertensive people [4].

Although multiple and carefully performed clinical blood pressure measurements may indeed reach a diagnostic power similar to that 24 h, this rarely is performed in practice, due to the very short duration of the physician visit [5]. Only ABPM allows blood pressure variability over day/night to be detected, therebing providing a parameter that may have an independent prognostic value, and it is confirmed its value in variability determination [6-7]. Moreover, only ABPM may cast some light in symptomatic episodes that occur over 24 h, either because of blood pressure increases or of blood pressure reductions. This approach may be usefully employed not only in the diagnosis of hypertension, but also when evaluating the rate and the severity of hypotensive episodes [5].

In "white coat hypertension", the home measurements, with adequate devices and carefully performed and with enough frecuency sufficient [8].

Preliminary evidence also suggest that the average 24h blood pressure obtained by ambulatory monitoring may be superior to casual blood pressure readings in treatment evaluation [9-10], because ABPM is largely unaffected by any placebo effect [11] and that 24 h BP rate have more reproducibility than office BP, avoiding the media regression phenomenon [12-13].

The "white coat effect" in treated hypertensives, may interfere in correct evaluation of treatment with clinical measurements.

ABPM is useful to investigate the new drugs effects. Few mathematical index, such as, trough/peak relation allow the proper evaluation of the antihypertensive therapy during 24h [14-15].

ABPM have advantages and disadvantages compared to clinic blood pressure [16].
Indications of ABPM
The ABPM indications for JNC [17] are the following:

- excluding “white coat hypertension”
- assessing apparent resistance to therapy
- episodic hypertension
- suspicion of hypotensive episodes
- autonomic dysfunction

Kaplan [18] thinks ABPM is useful in patients that cannot perform self-monitoring of BP, or when a more immediate diagnosis is necessary or to evaluate BP during sleep.

In my opinion there are two situations that ABPM have great value:

- pregnancy hypertension (diagnosis and therapeutic evaluation)
- diabetes mellitus patient, for early diagnosis, and strict treatment evaluation, because the importance of high BP in complications. In the autonomic dysfunction it is important the levels of BP in sitting and supine position are of great importance [19].

In order to simplify this description, we classify the ABPM indications as:

- A. Diagnostic
- B. Prognostic
- C. Therapeutic evaluation

It is necessary to perform a precise prognosis in hypertension to assure a correct diagnosis of situation in each patient.

A. ABPM in diagnosis
The definition of normal ABPM levels constitutes a challenging matter and it is important because the levels of BP in the diagnosis of hypertension are those that beneficial therapy are bigger than lowest levels [14].

Several studies have investigated these ABPM levels of normality in members of a general population [20].

In the studies [21-26] the 24 h mean systolic and diastolic pressures are lowest than clinical values and there are few differences between studies (Table 1).

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Elimination of observer bias/erro</td>
<td>Cost</td>
</tr>
<tr>
<td>Elimination of “white coat effect”</td>
<td>Disturbed sleep</td>
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<tr>
<td>Calculation of blood pressure loads</td>
<td>Cuff discomfort</td>
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<tr>
<td>Evaluation of dipping/non-dipping states</td>
<td>Inaccurate in atrial fibrillation</td>
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<tr>
<td>Ability to better assess BP variability</td>
<td></td>
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<tr>
<td>More comprehensive evaluation of therapy</td>
<td></td>
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<td>More reproducible over time</td>
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**Table 1:** Mean systolic and diastolic office pressures and its correlation with ABPM 24 H.
ABPM hypertension diagnosis was performed in different ways. Mancia et al [20] and ourselves [26] used the liminal levels of ABPM, matched the 140/90 mm Hg office values. These are:

- 129/79 in 24 h
- 131/85 in awake
- 116/70 during sleep

These are the normality levels [20].

Usually in practice the ABPM levels diagnostic of hypertension are 140/90 mm Hg in awake and 120/80 mm Hg during sleep. The ABPM percentages higher these values are denominated load. We have classified the individuals according to loads in 4 groups (table 2).

ABPM analysis contributes to a fundamental evaluation in order to perform a more precise prognostic and to establish the antihypertensive kind of treatment.

The parameters of BP than can be established for ABPM are:

- **hypertension pattern**: systolic, diastolic, systo-diastolic
- **load classification**: borderline, defined, sustained
- **ambulatory heart rate**
- **ambulatory pulse pressure**
- **ambulatory mean BP**
- **day/night BP changes**
- **circadian rhythms**
- **early morning BP rise**

### Table 2: Individual classification in load relation

<table>
<thead>
<tr>
<th>Load %</th>
<th>Category</th>
</tr>
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<tbody>
<tr>
<td>Between 0 and 19</td>
<td>normotensives</td>
</tr>
<tr>
<td>Between 20 and 39</td>
<td>borderline hypertension</td>
</tr>
<tr>
<td>Between 40 and 79</td>
<td>defined hypertension</td>
</tr>
<tr>
<td>Between 80 and 100</td>
<td>sustained hypertension</td>
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### B. ABPM in prognostic

The difference in cardiovascular risk among different categories generated by ABPM should be greater than the difference among risk categories generated by standard measurement of clinical BP [13].

The available observational studies on the prognostic value of ambulatory BP have been conducted in tertiary care centers on subjects with essential hypertension either untreated or treated at the time of execution of ABPM or in the general population [28-35].

Actually 10 parameters are considered in the prognostic ABPM evaluation (table 3).
Table 3. ABPM parameter in relation to risk

1. Ambulatory blood pressure as a continuous variable
2. Observed versus predicted ambulatory blood pressure
3. "White coat hypertension"
4. "White coat effect"
5. Day/night blood pressure changes
6. BP variability
7. Ambulatory heart rate
8. Ambulatory pulse pressure
9. Ambulatory mean BP
10. Rise of BP in early morning

1. Ambulatory blood pressure as a continuous variable.
An assessment of the prognostic value of ambulatory BP considered as a continuous variable has been carried out in the setting of the Ohasama Study [34-35].

During follow-up, which lasted an average of 5 years, there were 93 fatal cardiovascular events.

After adjustment for age, sex, smoking status, clinic BP, and use of antihypertensive medications, the risk of cardiovascular mortality was significantly increased in the highest quintile of the distribution of average 24h systolic BP, whereas no independent relation was found between clinic BP and mortality.

Ambulatory BP has been examined as a continuous variable in the Systolic Hypertension in Europe (SyS-Eur) study [36].

In that study, ambulatory BP monitoring was carried out at randomization in 808 untreated patients. Of these, 98 developed a cardiovascular event over the follow-up period.

After statistical adjustment for age, sex, office BP, active treatment, previous events, cigarette smoking, and residence in western Europe, night time systolic BP was an independent predictor of total, cardiac, and cerebrovascular events.

In a study, Redon et al [33] established in patients with resistant hypertension, with diastolic BP > 100 mm Hg, after an average follow-up period of 4 years, that the event rate was higher in the higher tertile of day time diastolic BP.

This study was criticized for Verdecchia and Schillaci [13], because limitations.

En the Helsinki study [37], with 3267 participants, a follow-up of 32 years show that the isolated diastolic hypertension is no related to risk. We think that the systolic hypertension is a better predictor of the cardiovascular risk than diastolic, but the diastolic hypertension may be important in the young hypertensive people.

2. Observed versus predicted ambulatory blood pressure
Ambulatory median pressure may be similar, lowest or higher that BP clinical [13].

Sokolow and Perloff and colleagues [28], the pioneers of clinical use of ABPM were the first to note that for any given value of clinic BP, the target organ damage in hypertension was more consistent in patients with higher-than-predicted ambulatory blood pressure than in those with lower-than-predicted ambulatory blood pressure.

Verdecchia et al [39] shown that cigarette smoking is an important determinant of higher-than-predicted ambulatory BP. The effect of smoking on ambulatory BP may lead to left ventricular hypertrophy [39]. Taken together, all these data suggest that higher-than-predicted ambulatory blood pressure should be considered a univariate prognostic predictor in subjects with stage I hypertension [13].

3. White coat hypertension
White coat hypertension, also referred to as office hypertension or isolated clinic hypertension, is generally defined by a persistently elevated office BP together with a normal pressure outside the office. Although the usual definition of elevated office BP is out of discussion (≥140/90 mm Hg) there is great deal of controversy
about the definition of normal BP outside the office [13] but there are few differences between studies and not have clinical significance. However, Verdecchia et al [39], have shown that no only the prevalence of white coat hypertension but also left ventricular mass at echocardiography end the prevalence of left ventricular hypertrophy increased markedly when swinging from more restrictive (lower) to more liberal (higher) limits of ambulatory BP normalcy used for the definition of white coat hypertension. The PIUMA dataset [41], indicates the importance of a restrictive definition of the upper normal limits of ambulatory BP in order to identify a population with characteristics of potentially cardiovascular risk. The prevalence of left ventricular hypertrophy, virtually absent below 120 mm Hg and very modest below 130 mm Hg (6 %), increased to 10.5 % when the limit was set to 140 mm Hg. Thus, even modest swings over a relatively narrow range of presumably normal or nearly normal ambulatory BP result in considerable differences in the prevalence of subjects with increased left ventricular mass and, because of its adverse prognostic value, potentially increased cardiovascular risk [13].

In a more recent analysis of the PIUMA database [41] support the use of a restrictive definition of white coat hypertension (i.e., average daytime ABP < 130/80 mm Hg), in order to identify the minority of subjects not at increased risk of cardiovascular morbid events when compared with the normotensive subjects.

4. White coat effect
The rise in intraarterial BP during the clinical visit is maximal during the 4 min of the visit, and disappears within 10 min and persist over several visits, even under treatment [13].

This phenomenon is referred to as "white coat effect". White coat effect and white coat hypertension are different entities that markedly differ in their definition, pathophysiologic, and clinical significance [13].

The white coat effect is a characteristic of hypertensive patients and the prognostic significance has not yet been established.

5. Day/Night blood pressure changes
Usually, the 24 h interval is divided into two periods of day and night (or wakefulness and sleep). Day and night may be defined using the waking and sleeping periods as resulting from the patient’s diary, or through arbitrarily defined fixed time intervals, both wide (6-22 h and 22-6 h). We use the former way.

A potential objection to the use of noninvasive ambulatory BP monitoring is that frequent cuff inflations could disturb sleep [42], with consequent possible overestimation of nigh-time BP. Independent laboratories, however, have shown that intraarterial profile is similar in the absence and in presence of concomitant noninvasive BP monitoring [43].

The dippers-nondippers classification is based on the hypothesis that for any given value of daytime BP, target organ damage and prognosis may be worse when the BP load is persistent throughout the 24 h than when it is limited to the daytime hours.

The changes day/night of BP show 4 patterns [44-46]:
- dippers: BP reduction 10-20 %
- nondippers: BP reduction 0-9 %
- hiperdippers: BP reduction > 20 %
- inverse dippers: BP do not fall, and in some cases may be higher than daytime readings

A large body of evidence is showing that:
- left ventricular hypertrophy [46]
- silent cerebrovascular disease [44]
- stroke [44]
- microalbuminuria [47]
- progression of renal damage [47]

are greater in subjects with blunted reduction in BP from day to night than in those with normal nocturnal BP reduction.

The number of lacunae had a J-shaped appearance, with an increase of lacunae in extreme dippers as compared with dippers, probably as a result of nocturnal hypotension with consequent cerebral ischemia as a
result of defective autoregulation of cerebral blood flow [13].

Like all categorizations of continuous variables, the dipper- nondipper classification is open to criticism [48-49], but we think that the principal problem is defined for the reduction of systolic, diastolic or mean BP [50].

Taken together, all these findings indicate that the assessment of day-night BP variability through the use of 24 h ABPM is important from a clinical standpoint in subjects with hypertension because it allows an improvement in cardiovascular risk stratification provided by clinic BP and other traditional risk markers [13].

6. Blood pressure variability

Parati et al [51] found that for every given value of ambulatory BP, the frequency and severity of target organ damage were greater in association with high BP variability than with a low BP variability, and this was corroborated later [52].

The PIUMA study [53] was incapable of corroborate this relation. But Mancia et al [54-55] to affirmed that this is was true.

This discussion is based in the speculation whether an increased BP variability is a cause or simply an index of target organ damage [13]. A unifying explanation could be that the overall impact of factors associated with vascular damage and reduced baroceptor sensitivity such as aging, severity of hypertension and diabetes could be reflected by a rise in BP variability detectable with noninvasive BP monitoring [13].

If the higher variability of BP is primary o secondary to reduced baroceptor sensitivity, we consider that is an important predictor of complications or of present target organ damage.

7. Ambulatory heart rate

There is strong evidence of an association between resting heart rate and subsequent incidence of cardiovascular and noncardiovascular complications [56].

Subjects with tachycardia are more likely to develop hypertension and atherosclerosis in future years [56]. A high heart rate is currently considered only an epiphenomenon of a complex clinical condition rather than an independent risk factor [56-59].

The heart rate was found to be a predictor of:

- development of hypertension arterial [56]
- myocardial infarction [56]
- cardiovascular morbidity in general [57]

The data related to sudden death were particularly impressive, especially in the Framingham study, in which a sharp upward trend in mortality was found in the men divided by quintiles of heart rate [58].

In the CASTEL study [50] the relation between heart rate and mortality was particularly strong for sudden death.

Experimental evidence suggest that high heart rate should be regarded as a pathogenic factor in the induction of the risk as well [56].

In fact, tachycardia favours the occurrence of atherosclerotic lesions by increasing arterial wall stress, and impairs arterial compliance and distensibility [61].

Heart rate can be considered as a marker of an abnormal clinical condition [62] and is correlated with BP, degree of obesity, cholesterol, triglycerides, postload glucose, and fasting insulin [62].

In other words, subjects with a fast heart rate exhibited the features of the insulin resistance syndrome and it is easy to understand why subjects with tachycardia develop atherosclerosis and cardiovascular events [61]. Recent results obtained for Palatini [56] suggest that upper normal value of heart rate should be set at 85 bm.

8. Ambulatory pulse pressure

The basic mechanism of the rise in pulse pressure with age is believed to be the progressive stiffening of
large elastic arteries [64].

A significant association has been noted in several studies between pulse pressure and subsequent rate of cardiovascular morbid events and such an association was independent of systolic and diastolic BP [65-68].

Mancia et al [69] showed that the rise in intrarterial systolic and diastolic BP during physician’s visit is 4-75 mm Hg (mean 27) and 1-36 mm Hg (mean 15), respectively. The larger rise in systolic than diastolic BP implies an increase in pulse pressure of about 12 mm Hg before to during the visit. Hence, the clinic pulse pressure may overestimate the normal levels of pulse pressure. Some cross sectional studies [69-71] suggest that ambulatory pulse pressure correlate with organ damage more closely than clinic pressure.

These data indicate that alerting reaction to office BP measurement weakens the relation between pulse pressure and total cardiovascular risk, and that ambulatory pulse pressure provide a more precise estimate of risk [13].

9. Ambulatory mean BP
The components of BP are [72]:

- steady: the mean BP
- pulsatile: the pulse pressure

In subjects with predominantly systolic and diastolic hypertension, ambulatory mean BP and pulse pressure exert a different predictive afford on the cardiac and cerebrovascular complications, although pulse pressure is the dominant predictor of cardiac events, mean BP is the major independent predictor of cerebrovascular events [73].

Several mechanisms may explain the dominant prognostic impact of the steady component of BP (ie, mean BP) on the subsequent cerebrovascular events [73].

The small penetrating end arteries, which supply the medial and basal portions of the brain and brain stem, seem to be particularly vulnerable to the adverse effects of high BP, inasmuch as these arteries arise directly from the main arterial trunks [73].

It is assumed that diastolic BP is also a steady component over which cyclic pulsatile stress does occur, it is worth noting that the association of diastolic BP with stroke is steeper than that with myocardial infarction and that the reduction in systolic and diastolic BP induced by antihypertensive treatment lower the risk of stroke to a greater extent than the risk of myocardial infarction [74-75].

So, it is important to measure the mean BP in ABPM.

10. Rise of BP in early morning
The typical circadian BP pattern of diurnal active subjects has two daytimes peaks. The first around 9:00 h and the second around 19:00 h, a small afternoon nadir around 15:00 h and a profound nocturnal nadir around 3:00 h [1].

A significant rise in BP before awakening was initially reported in 1978 [1].

The findings of an intraarterial BP on a large group of normal subjects reveal that the early morning rise in BP commences before awakening from nighttime sleep [1].

Considerable evidence indicates that sympathetic system drives the BP circadian rhythm and is the result of increased a-adrenoceptor activity.

Several studies shown a circadian rhythm in cardiovascular events [1]:

- myocardial ischemia
- myocardial infarction
- sudden cardiac death
- cerebrovascular events
- arrhythmic events
The occurrence of cardiovascular events is triggered by several pathophysiological conditions, particularly a sudden increase in:

- BP
- Heart rate
- Sympathetic activity
- Basal vascular tone
- Vasoconstrictive hormones
- Prothrombotic tendency
- Platelet aggregability
- Plasma viscosity
- Hematocrit

The BP reaches peak values in the morning, with a somewhat less prominent peak in the late afternoon or early evening.[1]

The morning arterial pressure surges may initiate plaque rupture, and the only way for diagnosis of this rise, that commences before awakening, is by ABPM [76].

C. ABPM to assess antihypertensive therapy

Over the past decade, there has been a marked increase in the utilization of 24-h ambulatory blood pressure for the evaluation of antihypertensive treatment and to assess new drugs for hypertension. The utility of ambulatory of ABPM in clinical pharmacology exceed this description.

Conclusions

Several observational prognostic studies had shown the ABPM value in hypertension. The analysis of the parameter above mentioned, derived in a precise diagnosis and prognosis.

Acknowledgments

I wish to thank Dra. Mariela García for her excellent assistance in manuscript translation.

Bibliografía


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Updating: 09/25/2003