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## A survey of recent reports on ambulatory blood pressure monitoring

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### Abstract

This article is a review of 25 publications on ambulatory blood pressure monitoring (ABPM) and the importance of its results in everyday clinical practice. These studies, published in 2008-2011, were selected from the Scopus database, but are also available in Pubmed. They were prepared by researchers from around the world, concerned with the problems of proper control of blood pressure (BP), and of abnormalities in the circadian pattern of BP in patients with arterial hypertension, diabetes mellitus or renal failure. In the first part of this article, I analyse publications focused on some nuances in the methodology of ABPM and recommend ways to avoid some traps, related not only to the individual patient but also to the device used and the technical staff. The next section is devoted to the advantages of ABPM as a diagnostic tool which enables clinicians to learn about patients' BP during sleep, and emphasizes the practical implications of this information for so-called chronotherapy. This section also presents some new studies on the prognostic value of ABPM in patients with cardiovascular (CV) risk. Some recent articles on the results of various methods of pharmacological treatment of arterial hypertension in different age

groups are then described. The observations presented in this article may be helpful not only for researchers interested in the chronobiology of the CV system, but also for general practitioners using ABPM.

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**Key words:** Ambulatory blood pressure monitoring; Arterial hypertension; Blood pressure; nondipping; Pharmacological treatment

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### INTRODUCTION

Although it has been almost 50 years since Maurice Sokolow first conceived, and then constructed, an apparatus for ambulatory blood pressure monitoring (ABPM), it has to be emphasised that initially this device was “a toy in the hands of scientists” rather than a routine diagnostic tool. It is only in the last 20 years, probably because of the increased popularity and availability of this equipment, that the number of publications describing experience with this method has grown year after year. While in the early 1990s only a few dozen publications on this topic were added to the databases of medical journals each year, in the 21st century almost one hundred new reports appear annually. The present paper is a review of those studies on ABPM from the last 4 years which are,

in the author's view, the most interesting from a practical point of view. The studies have been grouped thematically.

## METHODOLOGICAL TRAPS, OR HOW TO USE ABPM EFFECTIVELY

When it is set to 15 min intervals during the day and to 30 min intervals in the night, the device for ABPM takes about 100 measurements in one test session. The results of the monitoring are regarded as reliable when at least 90% of the results meet the criteria of properly taken measurements.

Researchers from the Family Care Center, University of Iowa Hospitals and Clinics (USA), decided to specify patient profiles which are associated with an insufficient quality of ABPM measurements. In order to define the profile of a patient for whom the percentage of valid readings was too low, the researchers analyzed 530 patients (age range 14-90 years) who underwent ABPM in 6 consecutive years. The analysis included age, sex, weight, height, body mass index (BMI), occupation, the distance from their home to the Clinic, the existence of diabetes mellitus or renal failure, as well as the values of arterial blood pressure (BP) measured by an office sphygmomanometer. The studied group was divided dichotomously into two: patients in whom the percentage of valid measurements was between 0% and 79%, and patients in whom that percentage was 80% and more (the threshold of a satisfactory quality of measurement was reduced by the authors of the study by 10%). In 84.7% of the patients, technically satisfactory readings were obtained, and analysis of the characteristics of patients in whom the percentage of artefacts, invalid readings, or measurements with technical problems was higher than 20%, indicated that diabetes mellitus, renal failure, and increased BMI are indicators which were associated with incomplete circadian ABPM session results. The authors of this study posed the question of whether individualisation or adaptation of this method, geared especially towards the patients demonstrating the above-mentioned factors, would improve the accuracy of the results of ABPM<sup>[1]</sup>.

Another methodological problem is connected not with the device, but with the human input to the process of conducting this examination. This concerns the precision with which the clinic technician inputs the patient's actual sleep time during the ABPM session. The importance of this issue was demonstrated in patients with type 1 diabetes by Delaney *et al*<sup>[2]</sup>. They compared the frequency of diagnosing the nondipper profile between a group where the actual sleep times were used and a group where preset sleep times were input into the software for evaluating the pressure profile. The diabetic patients for whom preset sleep times were used were significantly more frequently diagnosed with a nondipper profile than those for whom actual sleep times were given. When, in a second round of monitoring, the reproducibility of the nondipping phenomenon was evaluated in the group

with preset sleep times, it was apparent that, after actual reported sleep times were input into the software, only 36% of the patients actually showed disorder of the circadian rhythm of BP. The researchers recommend at least two rounds of BP monitoring in patients who were initially diagnosed with a nondipper profile, since conclusions from the first monitoring may have been the result of a methodological error.

ABPM is very time-consuming, and hence there is a temptation to ask to what extent shorter monitoring times are representative of the BP determined from a full 24-h ABPM session. In the study by Ernst *et al*<sup>[3]</sup>, doctors and statisticians evaluated more than one thousand ABPM examinations. After excluding the first hour of recording, the researchers divided these into 4-, 6-, and 8-h sessions, in order to compare the mean systolic BP over the shortened periods with the full 24-h session mean. Although the reduction of the BP monitoring to 6 h gave a mean BP value which was lower by about 5.41 mmHg, still, the shorter monitoring time produced values relatively close to the patient's mean obtained from a full 24-h session.

In 2011, Ernst *et al*<sup>[4]</sup> analyzed the same database of ABPM recordings in order to examine correlation of 6-h ABPM sessions with the results of full (24-h) BP monitoring across four clinical indications of referral, namely: (1) borderline hypertension; (2) evaluation of BP control on mono or dual therapy; (3) suspicion of white-coat hypertension; and (4) resistant hypertension. They found that using the 6-h systolic BP threshold of 137 mmHg for patients with indications of referral 1, 2, and 3 achieved high correlation for sensitivity and specificity (over 0.8), and using the threshold of 133 mmHg for patients with indication of referral 4 produced even higher values: at 0.93 and 0.83, respectively<sup>[4]</sup>.

In clinical practice it is rare for patients to undergo both electrocardiogram (ECG) monitoring and BP monitoring simultaneously. However, for a group of 239 patients in this not very comfortable situation, researchers from the University of Bonn (Germany) analysed changes in the ST segment in 24-h ECG Holter monitoring, whilst also monitoring circadian variability in BP<sup>[5]</sup>. In addition, the study analyzed ST segment depression induced in an exercise test on a cycle ergometer. ST-segment depression that met the criteria of myocardial ischemia was recorded in 29% of patients. In 7.6%, ST depression occurred only during the exercise test, in 9.6% only during the Holter monitoring, and in 11.8% it was detected by both methods. In the last subgroup, significantly lower threshold levels of BP and heart rate were observed at the onset of ST depression recorded in Holter monitoring during routine daily activities in comparison with the changes induced on a cycle ergometer. The results were 148 (Holter) mmHg vs 188 mmHg (ergometer) for the pressure, and 120/min vs 93/min for the heart rate, respectively. Although in several earlier studies it was suggested that Holter monitoring can partly replace an exercise test for the detecting of ischemic heart disease, in this study, where ABPM was also

used, it was shown that these two methods do not replace but complement each other.

Kayrak *et al*<sup>[6]</sup> from Selcuk University (Turkey) analyzed the importance of exaggerated BP response during exercise in diagnosing masked hypertension (normal BP in office measurements, elevated values at night). They found that, when patients performed an exercise test while undergoing ABPM, 41% of patients with this type of reaction to physical effort have masked hypertension. The authors therefore suggested that patients in this group should receive closer follow-up for hypertension<sup>[6]</sup>. Another condition associated with transient elevation of BP is the application and removal of the device for ABPM. As demonstrated by Yanovski *et al*<sup>[7]</sup> from the University of Pennsylvania (USA), this phenomenon is present not only in patients with hypertension (treated or untreated) but also in normotensive ones. The authors suggested that this psychophysiologic reaction should no longer be regarded as an artifact and ignored, and recommended the inclusion of the data from the initial and final measurements in the analysis of ABPM results<sup>[7]</sup>.

Standard deviation of serial BP measurements is a parameter which, in clinical trials, is calculated both for ABPM and for repeated casual office BP measurements (CBP). In the case of paediatric patients, for whom the frequency of occurrence of arterial hypertension is low and the effect of “white coat” syndrome is strong, the question arises whether ABPM would not be a more ethical form of checking the efficacy of antihypertensive drugs, and whether using this method in multicenter trials would allow researchers to reduce the cohort size, while maintaining the validity of the results.

A group of paediatricians-nephrologists from 9 countries who conducted clinical trials on the efficacy of ramipril in children with arterial hypertension tested the above-mentioned hypothesis, and analyzed the values of standard deviation for BP measured by means of the traditional method (CBP measurement) and also by ABPM. The efficacy of ramipril was proved by both methods but, as was to be expected, the divergence of BP measurements (as well as standard deviation) was much greater with the traditional method. Statistical simulation has shown that the use of ABPM in multicenter clinical trials on the efficacy of antihypertensive drugs in children would allow reduction of the number of patients required to be randomized to active treatment or to placebo by 75%<sup>[8]</sup>.

## ABPM AS A PROGNOSTIC INSTRUMENT, OR TECHNOLOGY ENTERS THE BEDROOM

In recent literature there are many studies concerning the prognostic value of the results of ABPM. These studies concern not only the patients of doctors with narrow specializations [e.g., nephrologists who take care of patients after kidney transplantation or electrocardiologists who control patients with implanted cardioverter-defibril-

lators (ICD)], but also patients from the daily practice of internists and family doctors, who are under medical care because of common diseases such as arterial hypertension and diabetes mellitus.

Krmar *et al*<sup>[9]</sup> from the Karolinska University Hospital (Sweden) evaluated the possibilities for early diagnosis of arterial hypertension in children after a kidney transplantation (the mean age of the recipients was 10 years) who were followed up for approximately 4 years ( $4.3 \pm 2.2$ ). They compared the frequency of diagnosing hypertension in this high-risk group following office BP measurements with the more recent period when regular ABPM performed at least once a year became the routine policy. In the “historical” period (the authors’ own term), hypertension was diagnosed on average 6 years after the transplantation, whereas with regular ABPM the decision to start or intensify antihypertensive treatment was made much earlier in 27 out of 37 cases (73%), significantly improving control over this risk factor in this young age group<sup>[9]</sup>.

The study by Paoletti *et al*<sup>[10]</sup> from Genoa (Italy) also concerns patients after kidney transplantation. Here the patients were older renal transplant recipients (aged 28-71 years), and the aim of the study was to examine the possibilities of an early diagnosis of renal graft damage. The researchers compared the classic markers of an adverse course after a kidney transplant (serum creatinine, daily proteinuria, triglycerides, immunological markers) with the results of 24-h ABPM. It turned out that the values of diastolic BP during the night and the initial creatinine concentrations were the only strong predictors of creatinine level a year after the surgery, while daytime systolic BP allowed them to predict intensified daily proteinuria. The authors concluded, somewhat surprisingly, that ABPM is the most reliable diagnostic method available to evaluate the course of the disease in renal transplant recipients. Similarly, Beltrán *et al*<sup>[11]</sup> from Valencia (Spain), observing the results of ABPM among kidney transplant patients, reported that “poorly controlled hypertensives” were older ( $54 \pm 9$  years *vs*  $45 \pm 13$  years) than “well controlled hypertensives”, received grafts from older donors ( $56 \pm 15$  years *vs*  $45 \pm 17$  years), had higher serum creatinine concentrations ( $1.7 \pm 0.5$  mg/dL *vs*  $1.4 \pm 0.4$  mg/dL) and more advanced proteinuria ( $0.3$  g/d *vs*  $0.18$  g/d). The large prevalence of uncontrolled nocturnal hypertension had a very strong impact on the abnormal result of ABPM in these patients<sup>[11]</sup>.

A further attempt to use ABPM results as a prognostic tool was made jointly by gynecologists and hypertensiologists from two Polish medical centers (Kraków and Gdańsk). The article by Liro *et al*<sup>[12]</sup> describes a group of 123 pregnant women with gestational hypertension (in most cases, this was their second pregnancy). For these women, the ABPM result was prognostic of the risk of premature delivery, because increased BP values during this examination were inversely correlated with the duration of the pregnancy and the child’s birth weight<sup>[12]</sup>.

Stratification of the risk of death is one of the most



important challenges for electrocardiologists who qualify patients for ICD in cases of dilated cardiomyopathy. An interesting method of death risk evaluation, proposed by the group of Antonini *et al*<sup>[13]</sup>, from Rome (Italy), was tested on a group of 105 patients after the ICD implantation. All the patients in this study had left ventricular ejection fraction  $\leq 30\%$ , and at 12-mo follow-up this parameter had no prognostic value for end-points such as death or hospitalization because of exacerbation of heart failure. Cox regression analysis revealed statistical significance for the prognostic value of the combination of the patient's age and the mean values of the 24-h systolic and diastolic BP. A prognostic index calculated in this simple manner was, therefore, proposed:  $(120 - \text{age}) + (\text{mean 24-h systolic BP} + \text{mean 24-h diastolic BP})$ .

Using this index it was shown that 61% of patients in whom it was  $\leq 220$  had end-points during the follow-up, while the percentage was significantly lower (12%) for patients whose index was  $> 220$ <sup>[13]</sup>.

The next group of studies concern patients with diabetes mellitus and arterial hypertension who are seen on a daily basis by a larger number of doctors.

A Japanese-American team Eguchi *et al*<sup>[14]</sup> tested the hypothesis that short-term BP variability and an abnormal circadian BP profile evaluated by ABPM help to predict the risk of cardiovascular (CV) diseases in patients with type 2 diabetes mellitus. Three hundred such patients, who underwent ABPM, were followed for  $50 \pm 20$  mo. The researchers established the abnormalities of their initial profile (nondipper, reverse-dipper, or excessive morning BP surge) and calculated the standard deviations of ABPM, separately for the hours when the patients were awake and for the time when they were asleep. This study is different from previous publications in that the authors regard excessive diastolic BP variability during sleep-time and the mean diastolic BP value at night, and not the nondipper, or reverse-dipper profile or excessive morning BP surge, as parameters significantly correlated with CV episodes<sup>[14]</sup>. Similar conclusions can be found in the paper by Leitão *et al*<sup>[15]</sup> from Brazil. They compared the prognostic value of an abnormal circadian BP profile with that of mean BP values during the day and at night, in order to assess the risk of microvascular target organ damage diagnosed by means of ophthalmoscopy, through increased proteinuria, or during echocardiographic examination of left ventricular hypertrophy in 270 patients. Again, it was not the circadian profile, but the night-time BP values that were correlated with the presence of hypertensive angiopathy, whereas cardiac hypertrophy and increased microalbuminuria were correlated more strongly with elevated systolic BP means than with night/day BP ratios<sup>[15]</sup>.

The work by Bouhanick *et al*<sup>[16]</sup> from Toulouse (France), also shows how important night-time BP values are for determining the risk of CV death, myocardial infarction or stroke in patients with type 2 diabetes and arterial hypertension. These researchers compared a group of reverse-dippers with patients classified on the basis

of ABPM as nonreverse-dippers ("others") in terms of CV complications. Ninety-seven patients were followed up for a median period of 5.5 years (and after a median period of 2 years and 7 mo they had undergone another ABPM). More than half of the patients (53%) who were classified as reverse-dippers after the first ABPM experienced CV events, whilst these events were significantly less frequent in 29% of patients. The most important conclusion from that paper is, however, that there were significant differences between the patients as regards mean night-time systolic BP. In the group of reverse-dippers this was  $148 \pm 23$  mmHg, compared to  $142 \pm 19$  mm among the nonreverse-dippers. The researchers calculated that an increase in the mean night-time systolic BP of 10 mmHg was associated with a 35% increase in the risk of a CV event in diabetic patients with hypertension<sup>[16]</sup>.

Does this mean that in patients with type 2 diabetes we should administer ABPM more frequently before any therapeutic decisions are made, since night-time BP measurement provides us with so much essential information? Conversely, one might ask whether an oral glucose tolerance test should be administered more frequently in normotensive, non-diabetic subjects with decreased nocturnal BP reduction (nondippers), since Li *et al*<sup>[17]</sup> described a significantly higher prevalence of the nondipping pattern in subjects with impaired glucose tolerance (77.4%) when compared with those presenting normal glucose tolerance (52.8%).

The author of the next two articles on the prognostic role of the results of ABPM seems to have been guided by the principle that there are no healthy people, only those who have not been diagnosed. Soylu *et al*<sup>[18]</sup> from the Meram Medical School of Selcuk University in Konya (Turkey) examined people who considered themselves healthy (the so-called normotensives), and tried to find a correlation between an abnormal circadian BP profile and the echocardiographic parameters of left ventricular diastolic function and cardiac structural changes. He demonstrated that the nondipper profile was associated with diastolic function disorders and a tendency for longer isovolumic relaxation time<sup>[18]</sup>. In a later publication, also on normotensives, the same author demonstrated that an insufficient reduction of systolic BP at night-time and an increased morning BP surge (after waking up) lead not only to a significantly higher left ventricular mass index, but also to an increased urinary albumin excretion. The group of patients cited here suggests that an effective pharmacological attempt to restore the normal circadian rhythm of the BP could reduce the risk to the target organ, at least in the context of individuals with arterial hypertension<sup>[19]</sup>.

## ABPM AS A MEANS OF CONTROLLING THE EFFECTS OF TREATMENT, OR WHICH DRUG TO CHOOSE

Which drugs should then be used to restore the normal

circadian BP rhythm? It seems natural to reach for the hormone of the biological clock - melatonin. In our own study we established that in patients with coronary artery disease and an abnormal BP profile, melatonin can restore the dipper profile in only 35% of patients diagnosed as nondippers at the beginning of the observation. Doctors considering giving melatonin to patients of this type, who often take several antihypertensive drugs, must be warned that increasing the ratio of the difference between the mean systolic BP value during the day and at night-time can be achieved not only through lowering sleep-time systolic BP but also through increasing the mean active BP<sup>[20]</sup>. Researchers focusing on the chronobiology of the circulatory system have emphasized that the time at which the medication is taken is an important factor attempting to improve the circadian BP profile. This aspect of the problem was studied, by Takeda *et al*<sup>[21]</sup> from Japan who confirmed the beneficial effect of giving long-acting antihypertensive drugs in the evening (as opposed to giving it in the morning) not only on the normalization of BP values, but especially on the restoration of the physiological rhythm of this parameter<sup>[21]</sup>.

Researchers from Spain and Switzerland used ABPM to evaluate the effects of missing one dose of antihypertensive medication in previously untreated patients with mild hypertension who had started their therapy only recently. According to statistics, some 15% to 20% of patients with hypertension forget to take their medication approximately 3 times a month. The comparison was between valsartan 160 mg/d taken in the morning and enalapril 20 mg/d also taken on waking. Unlike enalapril, valsartan was shown to be a drug with a more sustained effect, and with no significant influence of one missed dose on the BP level<sup>[22]</sup>.

A similar comparison of the angiotensin receptor blocker, telmisartan, and the angiotensin-converting enzyme inhibitor, ramipril, was described in the article by Williams *et al*<sup>[23]</sup>. The observation of two groups of hypertensive patients (each group consisting of more than 800 patients) randomized to telmisartan (80 mg) or ramipril (5 or 10 mg) focused on improving the mean 24-h systolic BP and the diastolic BP during the final 6 h of the monitoring. These trials, known under the acronyms PRISMA I and PRISMA II, favoured sartan, as a drug with a longer, more sustained effect, unchanged throughout the 24-h period<sup>[23]</sup>.

What can we say about the efficacy of two types of sartans used in combination therapies in hypertensive patients over 80 years old, patients who are largely ignored in clinical trials? Fogari *et al*<sup>[24]</sup> used BP monitoring to compare the effects of valsartan/amlodipine combination treatment *vs* irbesartan/hydrochlorothiazide combination for 8 wk in such patients. Valsartan with amlodipine turned out to be equally effective in reducing BP, but offered additional advantages in terms of less pronounced BP variability related to changes in body position, and fewer metabolic disorders, mainly hyperuricemia<sup>[24]</sup>.

## CONCLUSION

In conclusion, I would like to describe the results of a study which is fascinating in that it involved a very large group of people (745 volunteers) and covered a very long observation period, thereby yielding a lot of data. Between 1989 and 2004 the researchers collected results of arterial BP monitoring in children (the mean age at the beginning of the observation was approximately 14), who, before they reached early adulthood (approximately 20 years of age), had undergone multiple repeated ABPM<sup>[25]</sup>. On average each volunteer had undergone about 12 ABPM sessions. In the analysis of the results the authors used the so-called tracking coefficient, which can be described as “the coefficient of repeating the first result”. Values of this coefficient in the range 0.3-0.59 were considered to indicate degree of stability of the given parameter, and values < 0.3 suggest very little stability of the measurement. While it was shown that the mean results of both pulse pressure measurement and day-time and night-time BP measurements were predictably reproducible throughout the years, the tracking coefficients for the circadian BP variability turned out to be surprisingly low. In order to evaluate circadian BP variability, the researchers used three methods: (1) The traditional division into dippers and nondippers depending on the ratio of the mean day/night systolic BP higher than 10%; (2) Calculation of the absolute difference between the mean day-time BP and the mean night-time BP; and (3) Expression of night-time decrease in BP as a percentage of day-time BP.

Each of these methods showed an unsatisfactorily low tracking coefficient. The reproducibility of the results for dippers *vs* nondippers has for years been a moot point among researchers dealing with the chronobiology of the circulatory system. However, previously no one had gathered a substantial amount of data about multiple ABPM measurements in such a large population. If the results of this study were to be confirmed in a group of adults or in groups of patients with arterial hypertension or with ischemic heart disease, then the division of patients into dippers and nondippers according to the current criteria would be seriously undermined if not invalidated, as signaled by the authors of the studies described in the earlier sections of this article.

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