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ORIGINAL ARTICLE

Prediabetes is associated with abnormal circadian blood pressure variability

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Blood pressure (BP) exhibits a circadian variation characterized by a morning increase, followed by a small postprandial valley and a deeper descent during nocturnal rest. Although abnormal 24-h variability (abnormal circadian variability (ACV)) predicts adverse cardiovascular disease (CVD) outcomes, a 7-day automatic ambulatory BP monitoring (ABPM) and subsequent chronobiologic analysis of the gathered data, permits identification of consistency of any abnormal circadian variation. To test whether normal overweight healthy men and women with prediabetes differed from subjects with normoglycemia in having ACV with a 7-day ABPM. Consent for a 7-day ABPM was obtained from subjects with family history of diabetes mellitus, who were participating in the screening phase for a randomized, double blind, placebo-controlled weight loss trial in prediabetics to prevent progression to diabetes mellitus. The automatic 7-day ABPM device recorded BP and heart rate every 30 min during the day and every 60 min during the night. Normoglycemic and prediabetic subjects matched for age, sex, race, BP, BMI, waist circumference and glycemic control, differed statistically significantly only in their fasting and/or 2-h postprandial serum glucose concentrations. Chronobiologically-interpreted 7-day ABPM uncovered no abnormalities in normoglycemics, whereas prediabetics had a statistically significantly higher incidence of high mean BP (MESOR-hypertension), excessive pulse pressure and/or circadian hyper-amplitude-tension (CHAT) ($P<0.001$). ACV detected with 7-day ABPM may account for the enhanced CVD risk in prediabetes. These findings provide a basis for larger-scale studies to assess the predictive value of 7-day ABPM over the long term.
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Introduction

Control systems, some rooted in biological rhythms, ensure optimal functioning in all living organisms, small or big, simple or complex. A broad spectrum of genetically anchored rhythms are built into bacteria[1] as well as humans.[2,3] Individual cells, tissues,[4] organs and organ systems all display dynamic, and partly endogenous, ultradian (less than 20 h long), circadian (20–28 h long) and even longer rhythms. Rhythmic control of blood pressure (BP) is not as well characterized as some others, such as the secretions from the endocrine glands.[5] This is partly related to the short duration of BP recording and the paucity of databases of normal variations permitting elucidation of abnormal variability.

Recognition of BP and heart rate (HR) variations is now possible with automatic ambulatory BP monitoring (ABPM) devices, recording these variables at programmable intervals during the day and night, assessing both the endogenous and exogenous variability, over spans varying from several hours, to days or weeks. Automatic ABPM capturing this normal and/or abnormal variability is an easily obtained measurement that is a far superior determinant of cardiovascular disease (CVD) risk, when compared to a spot BP and HR obtained in a doctor's office.[6] A 7-day ABPM delineates abnormal variations including decreased HR variability, excessive pulse pressure, circadian-hyper-amplitude-tension (CHAT), impaired vascular compliance and/or odd circadian BP timing (circadian ecphasia). These conditions have been shown to be independent risk factors for heart disease and stroke,[7,8] even in apparently healthy individuals without chronic disease.

Diabetes mellitus (DM) is a well-recognized CVD risk equivalent.[9,10] Obtaining tight glycemic control in DM has been known to reduce this elevated CVD risk.[11] Recent reports, however, indicate that the CVD risk remains high when serum glucose concentrations are greater than 100 mg per 100 ml.[12] The risk for CVD can be increased as early as, 15 years before the overt loss of glycemic control.[13] Healthy normal or overweight prediabetic subjects with an IFG (impaired fasting glucose) and/or IGT (impaired glucose tolerance), also have an increased CVD risk.[14]

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Prediabetes is associated with early carotid atherosclerosis,[15] coronary artery calcification,[16] as well as other vascular abnormalities. It is an integral part of the metabolic syndrome,[17] a cluster of risk factors with underlying insulin resistance and compensatory hyperinsulinemia.[18] Metabolic syndrome was significantly related in multivariate analysis to myocardial infarction (OR, 2.01; 95% CI, 1.53–2.64), stroke (OR, 2.16; 95% CI, 1.48–3.16), and myocardial infarction/stroke (OR, 2.05; 95% CI, 1.64–2.57), in both women and men.[19] These subjects with prediabetes or the metabolic syndrome are also prone to and at high risk for subsequently developing DM.

Thus, early detection of prospective CVD risk in normal, otherwise healthy, but metabolically disadvantaged individuals (prediabetes, prehypertension and metabolic syndrome) by noninvasive methods may help with the design of primary prevention strategies.

This study compares the circadian BP variability over 7 days in normal healthy disease-free normoglycemic subjects with subjects having prediabetes.

Materials and methods

Study design

Subjects with a family history of DM, participating in the screening phase for a randomized, double-blind, placebo-controlled weight loss trial in prediabetics to prevent progression to DM were invited to consent for 7-day ABPM. The Pennington Biomedical Research Center Institutional Review Board approved protocol and consent form, enabled us to obtain 7-day ABPM before the end of the screening span when the glycemic status of the subjects became known.

Study population

Healthy men and women between the age of 35–75 years, with a family history of DM and with no personal history of or treatment for type 2 DM.

Seven-day automatic ambulatory BP monitoring

An automatic ABPM device (Spacelabs Medical, Issaquah, WA 98027-7018) was programmed to record BP and HR readings at 30-min intervals during the day (0600–0000 hours) and 60-min intervals at night (0000–0600 hours) for 7 days. Data were downloaded into the database midway and at the end of the recording span. Subjects who consented for and wore the automatic ABPM for a span up to 7 days during the screening stage are included in this paper.

Glycemic status

A 2 h 75-gram oral glucose load tolerance test was administered to fasting (10 h minimum), diurnally active, nocturnally resting, subjects between 0800 and 1100 hours. Normoglycemia was defined as fasting blood glucose less than 100 mg per 100 ml and a 2 h post-75-gram oral glucose load blood glucose of less than 140 mg per 100 ml. Prediabetes was defined by either a fasting plasma glucose of >100 mg per 100 ml but <126 mg per 100 ml (IFG) and/or a plasma glucose of >140 mg per 100 ml but <200 mg per 100 ml (IGT) at 2 h post-75-gram oral glucose load. The 7-day ABPM records from normoglycemic subjects are compared with those from prediabetic subjects for this paper.

Data analysis

Automatic ambulatory BP monitoring data gathered at the Pennington Biomedical Research Center were electronically sent to the Halberg Chronobiology Center, University of Minnesota for data analysis. A summary in time, that is, a sphygmochron, was derived, yielding estimates of the rhythm-adjusted mean (MESOR: midline-estimating statistic of rhythm or M), of the circadian amplitude and the acrophase for systolic BP, diastolic BP, pulse pressure (PP), and HR. The double circadian amplitude (2A) represents the extent of predictable change within a day referring to the 24-h amplitude in a model consisting of two cosine curves with periods of 24 and 12 h. The acrophase is a measure of the timing of high values for systolic BP (SBP), diastolic BP (DBP) and HR.

Nonparametric estimates were as follows: (1) Percentage time elevation (PTE), adjusted to gender and age after the subject's data were stacked over an idealized 24-h cycle. (2) Timing of overall highest excess (StE, DtE and HtE), representing the times of overall highest excess (vs upper chronodesmic limit) for SBP, DBP and HR, respectively. (3) Hyperbaric and tachycardic indices, representing the area under the curve delineated by the subject-stacked profile when it was excessive (above) and over (upper) the chronodesmic limit.[20–23]

Day-night ratios were also computed for the record as a whole and for each day separately, for a classification in terms of 'dipping'. A negative day-night ratio was classified as 'reverse dipping'. A positive day-night ratio less than 10% or greater than 20% was classified as 'non-dipping' or 'excessive dipping', respectively, whereas a day-night ratio between 10 and 20% was classified as 'dipping'.

Statistical methods

The circadian characteristics (MESOR, double amplitude and acrophase) were compared with 90% prediction limits available from clinically healthy subjects of the same gender and age group. MESOR-hypertension was defined as a BP MESOR above the upper 95% prediction limit of peers matched by gender and age. PP was defined as excessive when it exceeded 60 mm Hg. CHAT was defined as a circa-

dian double amplitude of systolic and/or diastolic BP above the upper 95% prediction limit of peers matched by gender and age. BP ecphasia was defined as an acrophase of BP occurring outside the 90% prediction interval of peers when the HR acrophase occurred within the anticipated 90% prediction limits. HR variability was defined as deficient when the standard deviation of HR was below 7.5 beats per min.

The incidence of any of the above abnormal circadian patterns of BP and/or HR, overall and for each day separately, in terms of circadian characteristics and in terms of the day-night ratio, was determined in each group and compared using Fisher's exact test and Student's *t*-test.

Results

Twelve subjects underwent 7-day ABPM during the screening phase of a weight loss trial in prediabetes to prevent progression to DM. The glycemic control of the subjects was not known until after the completion of the 7-day ABPM that measured BP and HR every 30 min during the day and every 60 min during the night (there were three exceptions: two records spanned only 3 days and one record covered 6 days).

Out of the 12 subjects 6 had normal glucose tolerance, whereas the other 6 had prediabetes (IFG and/or IGT). These groups included overweight African Americans and Caucasians (1:1), men and women (4 men/2 women vs 3 men/3 women). The groups were well matched with no statistically significant differences in age (51 ± 4 vs $54 + 4$ yrs), BMI (28 ± 3 vs $29 \pm 1\,kg\,m^{-2}$), BP ($120 \pm 4/74 \pm 1$ vs $131 \pm 7/77 \pm 4$ mm Hg) or glycemic control as expressed by HbA1c (5.6 ± 1 vs $5.9 \pm 2\%$). The prediabetic group, however, trended towards a larger waist circumference (89 ± 5 vs 99 ± 2 cm, $P = 0.08$). Statistically significant differences in serum glucose concentrations were seen between the normoglycemic and prediabetic groups. This was seen both with fasting (95 ± 10 vs 101 ± 2 mg per 100 ml, $P = 0.04$) and 2 h (96 ± 10 vs 147 ± 14 mg per 100 ml, $P = 0.04$) post-75-gram oral glucose load (Table 1).

None of the subjects with normoglycemia had any abnormal circadian BP variation, whereas four out of six subjects with prediabetes had various abnormalities on 7-day ABPM ($P < 0.001$, Fisher exact test). Percent of 24-h records with abnormal circadian BP variability in normoglycemics[1–6] and prediabetics[7–12] is shown in Figure 1. Overall, 66.7% prediabetics had abnormal circadian BP variations, compared to none in normoglycemics ($P < 0.001$) (Figure 2).

Figures 3a, b and c depict the individual abnormal circadian BP variations, comparing 1-day with 7-day analyses. Figure 3a depicts the presence of MESOR-HTN (elevated average BP) 80% of time in prediabetic subject 11. Figure 3b exhibits the presence of excessive pulse pressure (PP above 60 mm Hg) in prediabetic subjects 7 and 12, 60 and 100% of time, respectively. Figure 3c shows the presence of CHAT (a circadian BP amplitude above the upper 95% prediction limit of healthy peers matched by gender and age) 100% of time (all days) in prediabetic subject 8. Thus, prediabetic subjects 7, 8, 11 and 12 (4 out of 6; 66.7%) exhibit some form of abnormal circadian BP variation, overall as well as on one or more days during the 7-day ABPM, whereas none of the normoglycemics had an overall abnormal pattern (Figures 3a, b and c).

Table 1 Subject characteristics

	Normoglycemic (n = *6*)	*Prediabetic* (n = *6*)	P-*value*
Ethnicity	3C/3AA	3C/3AA	—
Gender	4M/2F	3M/3F	—
Age (years)	51 ± 4	54 ± 4	0.55
BMI ($kg\,m^{-2}$)	28 ± 3	29 ± 1	0.54
Waist circumference (cm)	89 ± 5	99 ± 2	0.08
HbA1C (%)	5.6 ± 0.07	5.9 ± 0.19	0.24
Fasting glucose (mg per 100 ml)	95 ± 10	101 ± 2	0.044
2-h glucose (mg per 100 ml)	96 ± 10	147 ± 14	0.014
SBP (mm Hg)	120 ± 4	131 ± 7	0.19
DBP (mm Hg)	74 ± 1	77 ± 4	0.62
Resting HR (b.p.m.)	70 ± 4	63 ± 3	0.19
ABPM abnormality	0	4	0.001

Abbreviations: AA, African American; ABPM, ambulatory BP monitoring; BMI, body-mass index; C, Caucasian; DBP, diastolic blood pressure; F, female; M, male; SBP, systolic blood pressure.

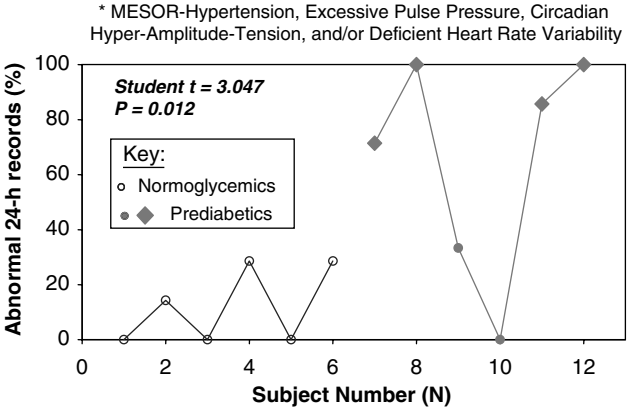

Figure 1 Percent of 24-h records with abnormal circadian blood pressure variability in normoglycemics and prediabetics.

Discussion

Cardiovascular risk assessment encompasses multiple facets both traditional (that is, DM, hypertension and/or dyslipidemia), and novel like early insulin resistance (prediabetes), early abnormal BP (prehypertension) and/or altered adipose tissue distribution

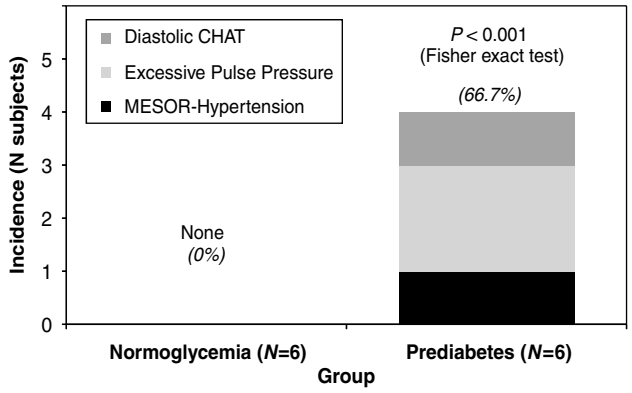

Figure 2 Abnormal circadian blood pressure variability in normoglycemia and prediabetes.

and function. A clinician responsible for the health maintenance of his/her patients is empowered for primary prevention in healthy disease-free individuals, notably if risk assessment is aided by easy, non-invasive methodology. By using the 7-day ABPM, this study attempts to provide data for such novel assessments.

A progressive relationship between glucose concentrations and cardiovascular risk has been known to extend below the diabetic threshold. Relative risk at a glucose concentration of 75 mg per 100 ml, when compared with risk at fasting glucose concentration of 110 mg per 100 ml and 2-h concentration of 140 mg per 100 ml was 1.33 (95% CI 1.06–1.67) and 1.58 (95% CI 1.19–2.10), respectively.[23]

In this study, healthy disease-free overweight subjects with glucose concentrations in the IFG and/or IGT category, when compared to matched subjects with normal glucose concentrations, exhibit a broad range of subtle circadian BP abnormalities, which increase their prospective CVD risk.

Normal BP values (BP of $<120/80$ mm Hg: based on the JNC VII classification of normal/desirable, prehypertension, stage I and stage II)[24] are a product of constant adjustment. A normal circadian variation is characterized by a 24-h rhythm including a morning increase, a small postprandial valley, and a deeper descent during nocturnal rest. Nocturnal blood pressures exhibit a variability of their own during the course of the night, exhibiting distinct, retiring (vesperal), night-time (basal) and preawakening (matinal) windows, that are characterized by blood pressure changes in normal individuals. The BP drops as one retires, reaches a minimum (dipping pattern) and rises sharply prior to awakening.[25] A diminished nocturnal BP fall portends an increased CVD risk.[26] A 10–20% fall in SBP during the course of the night is thought to be a normal daily variation, with 'dippers' having a 10–20% fall and 'extreme dippers' having a $>20\%$ fall. A proportion of patients (40%) are 'non-dippers' with $<10\%$ fall in nocturnal SBP, whereas others (13%) actually have a nocturnal increase in BP, 'the reverse dippers'. Aortic pulse wave velocity, a measure of

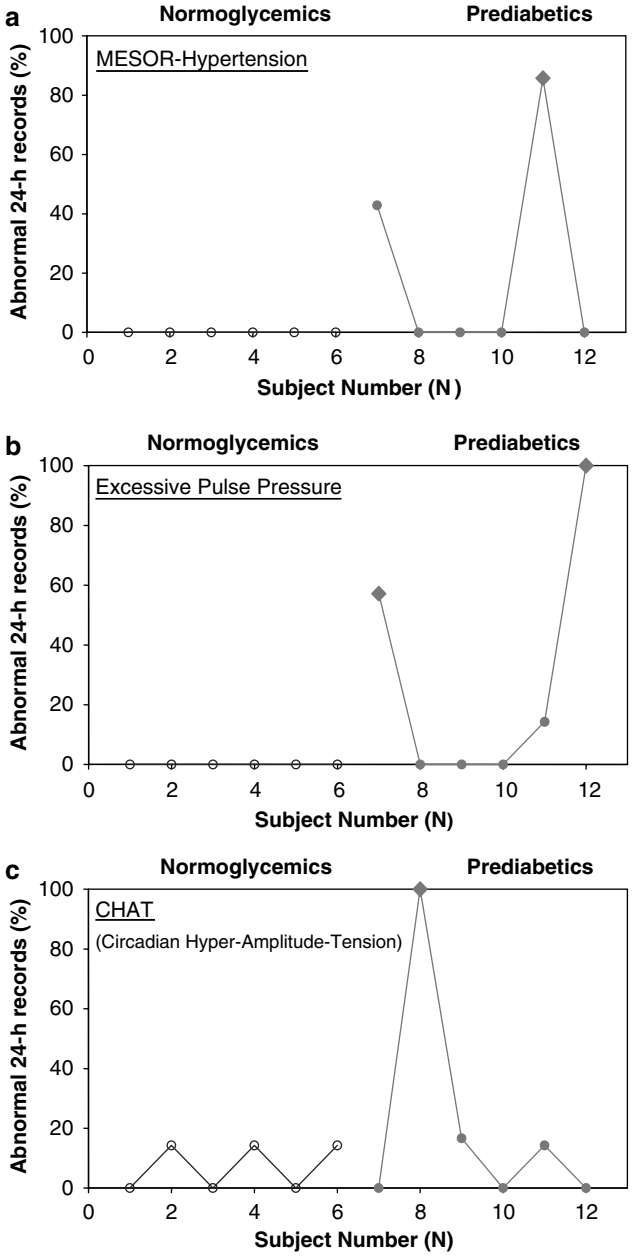

Figure 3 (**a**) Percent of 24-h records with MESOR-hypertension in normoglycemics and prediabetics. (**b**) Percent of 24-h records with excessive pulse pressure in normoglycemics and prediabetics. (**c**) Percent of 24-h records with circadian hyper-amplitude-tension in normoglycemics and prediabetics.

arterial stiffness, is increased in reverse dippers indicating an increased risk for CVD. Reverse dippers, in addition, have decreased HR variability and a wider pulse pressure[27] at night, suggesting an altered sympathetic tone. Moreover, these subjects tend to have left ventricular hypertrophy, microalbuminuria, cerebrovascular disease, congestive heart failure, vascular dementia and myocardial infarction.[28]

The Dublin Outcome Study[29] has shown that for each 10-mm Hg increase in night-time SBP, the mortality risk increases by 21%. Ambulatory arterial

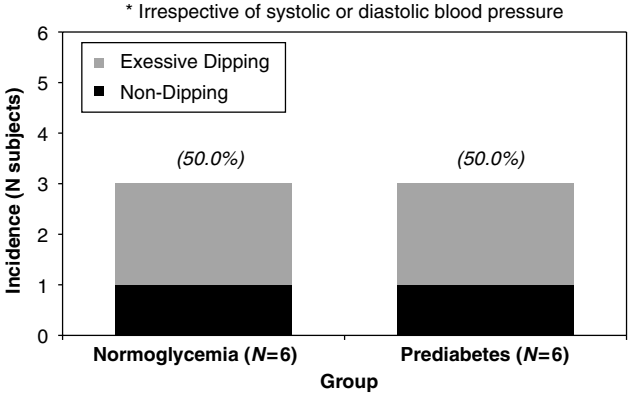

Figure 4 Incidence of abnormal dipping in normoglycemics and prediabetics.

stiffness index is a dynamic relationship between the DBP and SBP over a 24-h period. It allows for the estimation of arterial stiffness,[30] beyond the usual measure of PP, which reflects only a static difference between the SBP and DBP. Ambulatory arterial stiffness index is a strong predictor of stroke in normotensive individuals, whereas PP is a predictor of myocardial infarction in hypertensive patients.[31,32] Among all the CVD risk factors detected on ABPM, PP and SBP are most strongly associated with angiographically detected coronary artery calcification.[33]

Non-dipping, reverse dipping, nocturnal hypertension, nocturnal hypotension and autonomic failure are patterns that are easily recognized with ABPM, and with this recognition comes an opportunity for intervention and risk reduction.[34] The 7-day ABPM in this study used gender- and age-matched reference standards. A fit of a two-component model (of 24-h and 12-h cosine curves) to 7-day data often eliminated a transient circadian BP overswing.[35] Using the appropriate recording span, and a chronobiologic analysis, ACV can be detected worldwide.[36] A 7-day ABPM has greater diagnostic and prognostic benefit, due to the large number of data points gathered while subjects go through their activities of daily living, social and work routine, rest, recreation and sleep. No differences in nocturnal dipping (Figure 4) or the ambulatory arterial stiffness index was noted between the two groups in this study. The changes in circadian patterns of SBP, DBP, PP, HR and vascular compliance compared to a large body of matched normal patterns were, however, able to detect abnormal circadian BP variation.

The recognition of this abnormal circadian BP variability opens up opportunities for risk reduction in normal asymptomatic individuals, before the actual onset of clinical disease.

The two major findings in this study, namely the presence of abnormal BP variability in prediabetes and the higher discriminating power of a chronobiologic approach based on circadian characteristics by comparison with the day-night ratio used for a classification by 'dipping', are supported by previous studies. Based on a comparison of 24-h ABPM profiles from 117 patients with type 2 diabetes, 17 subjects with glucose intolerance, and 26 healthy peers, Sanchez *et al.*[37] found that prediabetes was associated with a larger circadian BP amplitude, in keeping with a higher likelihood of occurrence of CHAT, one of the abnormal circadian patterns observed in our study. An abnormal circadian pattern of BP was also associated with statistically significantly higher values of the left ventricular mass index (a marker of increased CVD risk) ($P<0.001$) in a study of 1179 untreated patients undergoing 24-h ABPM, when dipping failed to detect a difference,[38] c.f.[39]

Although the two groups were well matched for ethnicity, gender, age, BMI and glycemic control, the prediabetics trended toward a wider waist circumference ($P=0.08$). Waist circumference is an easily obtained clinical measure that estimates the visceral adipose tissue.[40] Increased visceral adipose tissue due to the altered distribution pattern impairs adipose tissue function, leading to an increased CVD risk.[41] This is primarily due to altered adipose tissue secretions with auto, para and endocrine effects on multiple metabolic pathways, including those that modulate BP.[42] It is plausible that this altered secretory activity of adipose tissue[43–45] unhinges the anti-inflammatory and pro-inflammatory adipokine balance, producing endothelial dysfunction, which over time leads to CVD.[46] This may be the underlying mechanism for the increased circadian BP abnormalities seen in the prediabetic subjects.

This study provides preliminary data that prediabetes is associated with subtle, but broad range of circadian BP abnormalities. These abnormalities due to their transient occurrence can be captured with 7-day ABPM. With elucidation of their cause, potential for modification in healthy individuals could reverse elevated cardiovascular risk.

What is known about this topic
- A progressive relationship between glucose concentrations and cardiovascular risk has been known to extend below the diabetic threshold
- Prediabetes is associated with an increased cardiovascular disease (CVD) risk

What this study adds
- Prediabetes is associated with subtle, but broad range of circadian blood pressure abnormalities
- These abnormalities due to their transient occurrence can be captured with 7-day automatic ambulatory BP monitoring (ABPM)
- The recognition of this abnormal circadian BP variability opens up opportunities for risk reduction in normal asymptomatic individuals, before the actual onset of clinical disease

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