Nocturnal blood pressure patterns in essential hypertensives: an overlooked cardiovascular burden

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(Index words: Ambulatory blood pressure monitoring, Abnormal nocturnal dipping, Nocturnal hypertension, Isolated nocturnal hypertension, Nocturnal hypotension)

Abstract

Introduction Understanding the diurnal variation of blood pressure (BP) is important in the management of hypertension.

Objectives Primary objectives of the study were to analyse the pattern of nocturnal BP in patients with essential hypertension who are already on treatment.

Methodology Cross-sectional descriptive study was conducted at cardiology unit Teaching Hospital Kandy, in 2015, in patients referred from the hypertensive clinic at Teaching Hospital Peradeniya. A consecutive sample of 100 essential hypertensives aged >18 years with stage I to III hypertension were included. Patients with a history of previous ischemic heart disease or cerebro-vascular events were excluded. Twenty-four-hour ambulatory blood pressure monitoring was performed in all patients after complete clinical evaluation.

Results Sample size was 100. Mean age was 60.86 ± 8.73 years. Twenty eight were male. In the sample 32 had normal dipping patterns. Out of the 68 with abnormal dipping, 45 had sub-optimal dipping, 19 had reverse dipping and 4 had extreme dipping. There were 72 patients with nocturnal hypertension, of them 29 (39.7%) had isolated nocturnal hypertension.

Conclusion A high prevalence of abnormal dipping, nocturnal hypertension and isolated nocturnal hypertension among our sample of patients with essential hypertension. Therefore, it is important to increase awareness and to consider ambulatory blood pressure monitoring to detect these abnormal nocturnal blood pressure variations.

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Introduction

Hypertension is a characteristic feature of functional dysregulation of the cardiovascular system. It is one of the main contributors of cardiovascular morbidity and mortality [1]. Therefore, prevention of hypertension related complications require maintaining the therapeutic range of blood pressure (BP). Ambulatory Blood Pressure Monitoring provides a good indication of the variations in circadian BP rhythm [2].

Nocturnal BP which is an important parameter can be evaluated using ambulatory blood pressure monitoring. Dipping of BP is a feature of the diurnal pattern of BP. Dipping patterns of nocturnal BP have been described previously according to the degree of BP drop [3,4]. There is evidence that the non-dipping pattern of diurnal BP variation is associated with poorer prognosis of cardiovascular events compared to those with normal dipping patterns [5].

Several studies have showed that more hypertensive end organ damage occur in patients with non-dipping patterns at night [6]. The novel clinical entity of isolated nocturnal hypertension (INH) is a new area of interest. These are people with elevated night-time BP with normal daytime BP [7]. This subgroup with isolated nocturnal hypertension have a higher incidence of target organ damage compared to nocturnal normotensives [7]. Since, patients with isolated nocturnal hypertension have lower or normal daytime BP, this group is not diagnosed and may present with end organ damage.

The objective of this study was to identify the pattern of nocturnal BP in patients with essential hypertension who were already on treatment. Study aims to identify presence of non-dipping patterns, nocturnal hypertension and isolated nocturnal hypertension.

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Methodology

A descriptive cross sectional study was conducted in 2015 at Teaching Hospital Kandy in collaboration with Teaching Hospital Peradeniya. Patients referred from the hypertensive clinic at Teaching Hospital Peradeniya to the Teaching Hospital Kandy were selected for the study and underwent ambulatory blood pressure monitoring and further evaluation. A consecutive sample of 100 patients were included in the study. Inclusion criteria were essential hypertension with stage I to III, without a history of previous ischaemic heart disease or cerebro-vascular events and normal serum creatinine. Pregnant patients were excluded from the study.

All patients were instructed to maintain a sleep diary and patients who had more than two wakeup events after falling asleep and patients with clinical evidence of sleep related breathing disorders were excluded. History was obtained and physical examination was carried out. Socio-demographic data, vascular risk factors, past medical history and recent laboratory investigations were obtained. All patients underwent electrocardiograms and two dimensional echocardiographic assessments. Standard office BP recording were obtained at the clinic.

Ambulatory blood pressure monitoring

A twenty-four hour ambulatory blood pressure monitoring was carried out in the non-dominant arm using an oscillometric portable monitor, Schiller BR-102®. The apparatus meets the standards of the British Hypertension Society and the United States Association for the Advancement of Medical Instrumentation.

Ambulatory blood pressure monitoring was performed in the patients' homes. All patients were asked to carry out normal activities of daily living but were advised to avoid vigorous exercise during the BP monitoring period. For ambulatory blood pressure monitoring, night time was defined as 2201 hours to 0700 hours and daytime was defined as 0701 hours hours to 2200 hours. The device was programmed to obtain a reading every 30 minutes from 7.00 a.m. to 10.00 p.m. and every 60 minutes from 10.01 p.m. to 7.00 a.m.

Definitions

Ambulatory normotension was defined as night-time blood pressure <120/70 mm Hg and a daytime BP <135/85 mm Hg. Nocturnal hypertension was defined as BP >120/70mmHg at night, which is caused by disturbed circadian rhythm. Isolated nocturnal hypertension was defined as night-time systolic BP ≥120 mmHg or diastolic BP ≥70 mmHg and a daytime BP <135/85 mmHg [8]. Isolated daytime hypertension was defined as daytime systolic BP ≥135 mmHg or diastolic BP>85 mmHg and a night-time BP <120/70 mm Hg. Day-night sustained hypertension was defined as night-time systolic BP ≥120 mm Hg or diastolic BP >70 mmHg and a daytime systolic BP ≥135 mmHg or diastolic BP >85 mmHg [7].

Dipping was defined as night-to-day BP ratio; sub optimal dipping (0.9 <ratio <1.0); normal dipping (0.8 < ratio <0.9); and extreme dipping (ratio <0.8) [3]. Night time rise of BP (reverse dipping) was defined as night to day BP ratio >1.0 [4].

Statistical analysis

Data entry and analysis were done using SPSS version 17.0. A p value of < 0.05 or 95% confidence limit was considered as significant. Continuous variables with a normal distribution were described as means with standard deviation. Between-group comparisons were performed using the Student t-test or the chi-square test, as appropriate.

The study protocol was approved by the Research Ethics Committee, Teaching Hospital Kandy. Written informed consent was obtained from all patients.

Results

Demographic characteristics

There were 100 subjects, 72 were females. The mean age of the sample was 60.86±8.73 years. Baseline characteristics of the study sample are illustrated in Table 1.

According to ambulatory blood pressure monitoring, mean day time systolic BP was 137±16.55mmHg and mean night time systolic BP was 127.93±18.4mmHg. The mean day time diastolic BP was 79.87±11.12mmHg and the mean night time diastolic BP was 73.40±11.24mmHg. Characteristics of ambulatory blood pressure and heart rate are shown in table 2. Systolic and diastolic BP variation during the day and night is illustrated in figures 1 and 2.

Table 1. Demographic characteristics of study sample

	Number (%) (n=100)
Age (mean±SD)	60.86 ± 8.73 years
Gender	
Male	28 (28%)
Female	72 (72%)
Pharmacotherapy	
Angiotensin Converting Enzyme Inhibitors	30 (30%)
Angiotensin Receptor Blockers	51 (51%)
Calcium Channel Blockers	27 (27%)
Diuretics	40 (40%)
Beta blockers	21 (21%)
Alpha blockers	13 (13%)
Co-morbidities	
Diabetes Mellitus	25 (25%)
Dyslipidemia	62 (62%)

Table 2. Ambulatory blood pressure monitoring and heart rate

	Mean ± SD
24-hour average systolic BP (mmHg)	135.37 ± 16.29
Daytime average systolic BP (mmHg)	137.00 ± 16.55
Night-time average systolic BP (mmHg)	127.93 ± 18.4
Percentage of night-time systolic BP reduction[a]	6.62%
24-hour diastolic BP (mmHg)	78.66 ± 10.83
Daytime diastolic BP (mmHg)	79.87 ± 11.12
Night-time diastolic BP (mmHg)	73.40 ± 11.24
Percentage of night-time diastolic BP reduction[b]	8.10%
24-hour heart rate (/min)	71.85 ± 10.42
Daytime heart rate (/min)	73.20 ± 10.56
Night-time heart rate (/min)	65.81 ± 10.67
Percentage of night-time heart rate reduction[c]	10.09%

[a] (Daytime SBP-Night-time SBP) / Daytime SBP×100

[b] (Daytime DBP-Night-time DBP) / Daytime DBP×100

[c] (Daytime HR-Night-time HR) / Daytime HR×100

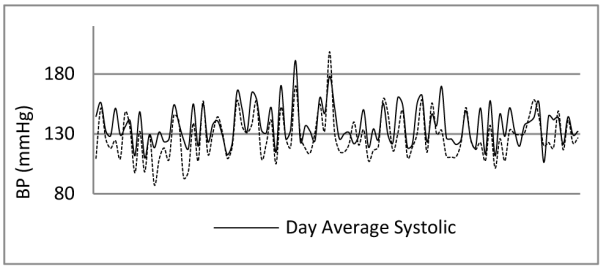

Figure 1. **Systolic BP fluctuation in the study sample.**

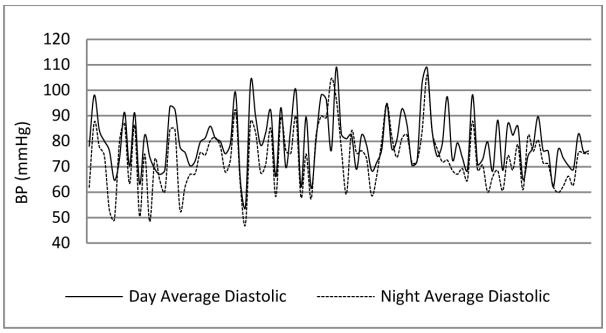

Figure 2. **Diastolic BP fluctuation in the study sample.**

BP dipping pattern and reverse dipping

In the sample 32 (32%) had normal dipping patterns. Out of the 68 with abnormal dipping, 45 had sub optimal dipping and 19 had reverse dipping. Four patients had extreme dipping. All 19 with reverse dipping pattern had nocturnal hypertension and 6 (32%) had isolated nocturnal hypertension. There was no statistically significant difference in the average nocturnal heart rate in reverse dippers (63.9±12.1 min^{-1}) compared to normal dippers (69.2±9.5 min^{-1}) (p=0.184).

Prevalence of nocturnal hypertension

Seventy three patients had nocturnal hypertension, 45 had day-night sustained hypertension and 2 had isolated daytime hypertension. Only 26 were normotensive (Table 3).

Isolated nocturnal hypertension

Among the 73 patients with nocturnal hypertension 29 had isolated nocturnal hypertension. The circadian rhythm of BP among patients with isolated nocturnal hypertension is illustrated in figure 3.

Patients with isolated nocturnal hypertension had significantly lower ambulatory day time pressure compared to other patients with nocturnal hypertension; systolic 126.8±9.3 mmHg vs. 151.6±11.6 mmHg, ($p<0.05$), day time diastolic 1±8.9 mmHg vs. 87.2±10.6 mmHg ($p<0.05$) and pulse pressure 50.8±9.0 mmHg vs. 64.1±12.4 mmHg (p=0.482). The fluctuations of daytime systolic BP and diastolic BP among patients with nocturnal hypertension with and without isolated nocturnal hypertension is shown in figure 3.

Patients with isolated nocturnal hypertension had low manual office BP recordings for both systolic and diastolic BP, compared to patients without isolated nocturnal hypertension. The difference was statistically significant (Table 4). However, statistically significant difference was not identified in average nocturnal and day time heart rate among patients with isolated nocturnal hypertension compared to patients without isolated nocturnal hypertension.

Nocturnal hypotension

Four had extreme dipping. In these patient the lowest systolic BP was 87.5 mmHg and diastolic BP was 48.5 mmHg. The variability of nocturnal BP distribution is shown in Table 5.

Heart rate variability in nocturnal hypertension

Average day time heart rate was 73±11min^{-1} in patients with nocturnal hypertension and 73.6±9.4 min^{-1} in patients with nocturnal normotension. The difference was not statistically significant (p=0.733). Similarly, the average night-time heart rate of nocturnal hypertensives was 65.5±11min^{-1} and nocturnal normotensives 66.7±9.3min^{-1}. The difference was not significant (p=0.628).

Fourty seven were categorised as heart rate non-dippers, defined as those who showed a nocturnal dip in heart rate of less than 10% of the day time value. Heart rate non-dippers had a significantly higher average nocturnal systolic BP compared to heart rate dippers (130.8±19.5mmHg vs. 125.4±17.1 mmHg, p<0.05) and diastolic BP (76.1±10.9 mmHg vs. 71±12.1 mmHg, p<0.05).

Table 3. Comparison of office BP values in patients with and without isolated nocturnal hypertension

Parameters	*Isolated nocturnal hypertension (n=29)*	*No isolated nocturnal hypertension (n=71)*	*P Value*
Mean office systolic BP (mmHg)	126.5±8.9	139±17.4	P<0.05
Mean office diastolic BP (mmHg)	75.6±8.6	79.9±11.4	P<0.05
Mean Daytime heart rate (min^{-1})	72.4±12.6	73.5±9.7	0.632
Mean Night-time heart rate (min^{-1})	65.6±13.1	65.9±9.6	0.898

Table 3. Variability of nocturnal BP

Nocturnal systolic BP (mmHg)	*Prevalence*	*Nocturnal diastolic BP (mmHg)*	*Prevalence*
≥120	63%	≥80	30%
110-119	24%	70-79	32%
100-109	7%	60-69	26%
90-99	4%	50-59	9%
80-89	2%	40-49	3%

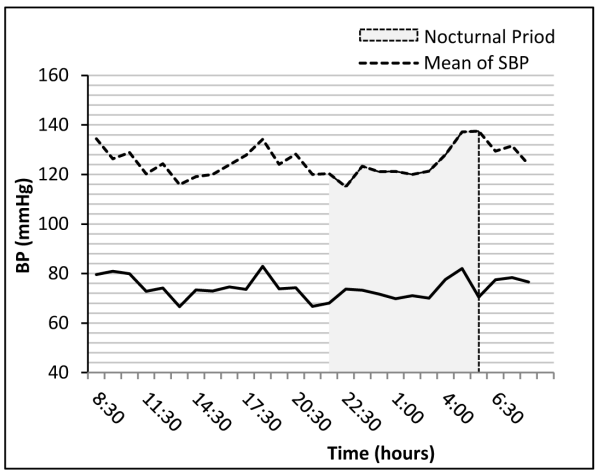

Figure 3. **Circadian rhythm of BP in patients with isolated nocturnal hypertension.**

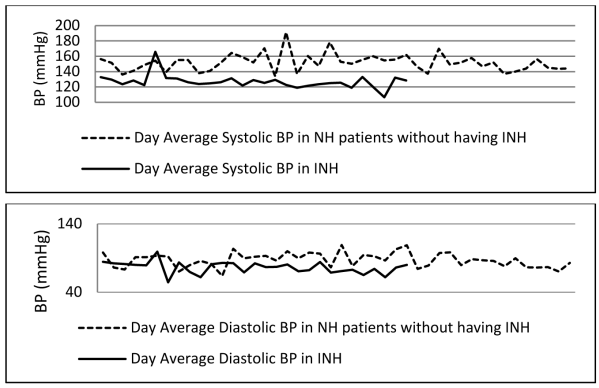

Figure 4. **Systolic BP fluctuation in patients with nocturnal hypertension with and without isolated nocturnal hypertension**

INH – isolated nocturnal hypertension;
NH – nocturnal hypertension

Discussion

Abnormal dipping pattern and nocturnal hypertension

In normal people BP shows diurnal variation, where the average nocturnal BP is substantially lower than daytime [9]. Disturbance of this circadian rhythm may result in adverse cardiovascular outcomes. There is evidence that nocturnal BP levels are more accurate in predicting mortality and morbidity due to hypertension and this is independent of mean BP and daytime BP values [10,11]. Population based studies as well as studies of hypertensive cohorts show that elevated nocturnal BP indicate unfavourable cardiovascular outcomes [5,13-16].

Endothelial dysfunction has been described among the non-dippers [6]. A study by Higashi *et al*. has demonstrated, the endothelium-dependent vasodilation induced by acetylcholine is impaired in non-dippers to a greater extent than dippers [6]. Furthermore, they demonstrated that nitric oxide production per se is reduced in non-dippers.

A study by de la Sierra *et al.* reported prevalence of non-dipping pattern of 47.9% -58.7% [17]. de la Sierra *et al.* included patients with coronary artery disease and chronic kidney disease; we did not include these patients in our study. We found a slightly higher prevalence (68%) of non-dipping pattern among patients with essential hypertension. This may indicate that patients with essential hypertension have higher prevalence of nocturnal hypertension and physicians generally miss this unless they carry out ambulatory blood pressure monitoring. Since evidence shows that patients with abnormal dipping patterns have more complications it is important to consider ambulatory blood pressure monitoring in patients with hypertension.

Early identification of nocturnal hypertension might be clinically relevant for BP control to prevent hypertensive end-organ damage, especially in patients with high risk of cardiovascular complications. Since nocturnal hypertension can only be diagnosed by ambulatory blood pressure monitoring it is largely undetected because of its limited use in clinical setting. Widespread use of ambulatory monitoring may be limited due to financial constraints. Therefore, we would like to recommend the practice of ambulatory blood pressure monitoring at least in high risk patients.

Chatzistamatiou *et al*. reported prevalence of nocturnal hypertension of 58%. This study included newly diagnosed, never treated, uncomplicated hypertensives [18]. We found a prevalence of nocturnal hypertension of 72% in patients already on treatment. Chatzistamatiou *et al.* also reported that patients with nocturnal hypertension have an exaggerated inotropic response during exercise, increased arterial stiffness, and elevated serum uric acid levels. All these support the hypothesis that elevated nocturnal BP has negative effects on the cardiovascular system resulting in poor prognosis [18].

If patients are diagnosed with nocturnal hypertension physicians should pay attention to the night time drug dose adjustment and alteration of current medications to achieve normal or near normal normotension at night. It may require be changing current treatment and adoption of non-pharmacological methods such as cutting down night time salt intake, engaging in exercise in the evening). Ambulatory blood pressure monitoring should be repeated to identify the response to treatment changes.

Isolated nocturnal hypertension

Analysis of a multi-ethnic international database on ambulatory blood pressure monitoring reported higher prevalence of isolated nocturnal hypertension in Chinese (10.9%), Japanese (10.2%), and South Africans (10.5%) than in Western Europeans (6.0%) and Eastern Europeans (7.9%) [7]. However, we found a higher prevalence (29%) of isolated nocturnal hypertension in our sample. This is an important finding and the reasons for the high prevalence of isolated nocturnal hypertension should be investigated.

Patients with isolated nocturnal hypertension have more severe end-organ damage than normotensive subjects [8]. Although they have much lower day time ambulatory BP compared to day-night sustained hypertensive patients, the rate of hypertensive end-organ damage is similar [7]. Because these patients have normal daytime BP, the diagnosis of isolated nocturnal hypertension is not possible using conventional office BP values.

Since patients with isolated nocturnal hypertension have normal day time BP, the diagnosis should be suspected in anyone with possible hypertensive target organ damage (eg. left ventricular hypertrophy, myocardial infarction or stroke at a young age) with normal office BP readings. Ambulatory blood pressure monitoring should be considered in high risk patients. It is well-established that, controlling BP using antihypertensives reduce the risk of adverse cardiovascular events, such as coronary artery disease and stroke [19,20]. Similarly, physicians should treat isolated nocturnal hypertension with antihypertensives.

There are no detailed guidelines on the treatment of isolated nocturnal hypertension other than description regarding selection of medication, dosage frequency and use of bed time extended release preparation.

Nocturnal hypotension

Despite the benefits derived from lowering high nocturnal BP, there is increasing evidence that extreme reduction of nocturnal BP may increase cardiac and cerebrovascular adverse outcomes. Therefore, physicians should be aware of the dangers of lowering nocturnal BP to extremely low levels.

In our study, only 4 had nocturnal hypotension. This

may not be identified by conventional office BP monitoring. If there is nocturnal hypotension physicians should alter medications, cutting down the nocturnal dose and using extended release preparations at night to prevent extreme reduction of nocturnal BP.

Heart rate variability in patients with nocturnal hypertension

Heart rate is mainly determined by the balance between sympathetic and para-sympathetic neuronal tone [21]. The autonomic nervous system also regulates the central and peripheral vascular tone which has a major impact on the BP [22]. In our study, the average nocturnal systolic BP and diastolic BP of heart rate non-dippers was elevated compared to heart rate dippers. This indicates the importance of overall autonomic tone in the management of hypertension. Therefore, ambulatory blood pressure monitoring derived heart rate also should be considered in the management of nocturnal hypertension and isolated nocturnal hypertension. It will be interesting to see the favourable effects of lowered nocturnal heart rate on the nocturnal BP of patients with nocturnal hypertension in future studies in our patients.

Our study had several limitations. One is sampling bias due to recruitment of consecutive patients. Also subgroup analysis according to comorbidities such as diabetes mellitus or obesity or according to medication prescribed could not be carried out because of the small sample size. Another limitation is the larger number of females in the sample probably because we excluded patients with coronary artery disease.

Conclusions

In the study, we found a high prevalence of abnormal dipping patterns, nocturnal hypertension and isolated nocturnal hypertension among patients with essential hypertension who are already on treatment. This shows the importance of ambulatory blood pressure monitoring to identify these phenomena. However, in limited resource settings, we would suggest ambulatory blood pressure monitoring at least in high-risk patients.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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