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Research Article

THE ASSOCIATION OF AMBULATORY BLOOD PRESSURE PROFILE ON CARDIOVASCULAR REMODELING IN PATIENTS WITH ESSENTIAL HYPERTENSION

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ABSTRACT

Introduction: Blood Pressure (BP) of an individual has a strong implication for cardiac remodeling in different level of tissues even from the cellular level.
Objectives: The study was aimed to explore the association of different ambulatory BP variables on echocardiographic evidences of cardiac remodeling, diastolic dysfunction and Ambulatory Arterial Stiffness Index (AASI).
Methodology: A descriptive cross-sectional study was conducted at Cardiology Unit, Kandy in 2015, recruiting consecutive sample of 100 essential hypertensive patients with normal renal functions and no history of ischemic cardiovascular events. Ambulatory BP monitoring and echocardiographic evaluations were performed in all the patients.
Results: The study sample included 100 subjects; consisted of 72% females (mean age 60.86±8.73 years). There were 48% had mild Left Ventricular Hypertrophy (LVH), 27% had moderate LVH and 7% had severe LVH. IVS thickness had a positive correlation with 24-hour average ambulatory systolic BP ($r=0.3$, $p<0.01$) and 24-hour average ambulatory diastolic BP ($r=0.28$, $p<0.01$). There was a positive correlation found between average day time systolic BP and Left Ventricular Mass (LVM) ($r = 0.29$, $p < 0.006$) and average nocturnal systolic BP ($r=0.34$, $p=0.009$). Similarly, there was a statistically significant positive correlation noted between day time average diastolic BP and LVM ($r=0.269$, $p=0.008$) and average nocturnal diastolic BP ($r=0.4$, $p=0.024$). In the study sample 23.68% and 76.31 % had grade I and II diastolic dysfunction respectively. AASI showed a positive correlation with 24-hour average systolic BP ($r=0.02$ $p=<0.001$), average nocturnal systolic BP ($r=0.357$, $p<0.001$) and average pulse pressure ($r=0.562$, $p<0.001$).
Conclusion: Occurrence of altered LV geometry, as a marker of cardiac remodeling in hypertension and AASI, best correlate with several ambulatory BP parameters. Therefore, evaluation of BP by ambulatory monitoring can be used as a one of a sensitive tool for the evaluation of hypertensive cardiac remodeling.

INTRODUCTION

Blood Pressure (BP) of an individual has direct impact over remodeling of various cardiac tissues even from the cellular level.[1] It may turn into adverse cardiac remodeling in pathological instances, finally results-in many cardiovascular end organ damages.

The process of cardiac remodeling has understood as alterations in size, geometry, shape, composition and function of the heart as a result of cardiac load or injury[1]. Remodeling of the Left Ventricle (LV) is often seen in hypertensives and has been considered as a pathological adaptive response to hemodynamic overload imposed by systemic hypertension[2]. However, in pathological instances, it has been recognized as a significant risk factor for sudden cardiac death, acute myocardial infarction, and congestive heart failure in these patients indicating bad prognosis[3]. Therefore, the importance of identifying the various patterns of remodeling in hypertensive patients in their early clinical course is widely justified[4].

As with the understanding of BP as a dynamic parameter, ever more interest is focused over the various patterns of diurnal

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variation and its relationship with cardiac remodeling. It has been evident that, the ambulatory BP parameters are reported to be better correlated with hypertrophic LV response and more predictive of prognosis than of office BP values[5]. Similarly, the abnormal fluctuation of nocturnal BP is one of the unique features that have been linked to the outcome of various cardiovascular end organ damage[6]. Interestingly, higher LV mass, and increase left atrial diameter have been reported in non-dipper hypertensive patients[7] suggesting this relationship. Since that, understanding of the diurnal BP may be providing an additional information of an individuals' cardiovascular prognosis.

Diastolic dysfunction is an entity that had gained more interest in current era of cardiology. Sine diastolic dysfunction is directly related to the hypertrophic response of the LV[8], it may also have linked to the parameters of dynamic variation of BP.
The ambulatory arterial stiffness index (AASI) is a novel indicator of arterial stiffness which shows the dynamic relationship between systolic and diastolic BP[9]. Additionally, more evidences are claiming, it is a better estimator of atherogenic potential of an individual as well[10]. It has been well recognized that large-artery stiffness is indicative of target organ damage in various settings of hypertension, including essential hypertension[11]. Ambulatory Blood Pressure Monitoring (ABPM) has emerged as a versatile tool in the prediction of large arterial hemodynamic load as an effective on-invasive method in current medical practice[12].

Hear in our study, we have aimed to explore the influence of ABPM variables in a group of chronic essential hypertensives on their cardiac remodeling in three different aspects. The first aspect of the study was to explore the association of different ABPM variables on echocardiographic evidences of cardiac remodeling, especially the hypertrophic LV response. Secondly, to evaluate the occurrence of diastolic dysfunction among them and finally to evaluate the relationship of AASI in relation to circadian BP variability.

MATERIAL AND METHOD

The study subjects consisted of 100 consecutive patients with essential hypertension. Study enrolment criteria included; patients who were above 18 years with stage I to III hypertension[13] with normal renal functions and having no previous history of coronary or cerebrovascular events. Patient with essential hypertension complicated with pregnancy were excluded from the study. Addition to that, the patients with significant valve disease, impaired global or segmental wall motion and who had past history of cardiomyopathies were excluded from the study.

Informed written consent was obtained from all participants. The study protocol was approved by the Research and Ethical Review Committee, Teaching Hospital Kandy, Sri Lanka.

Ambulatory blood pressure monitoring

A twenty-four-hour ABPM was obtained by oscillometric portable monitor at the non-dominant arm. The ABPM device reached the standards of the American National Standards Institute. All the patients were allowed to engage in their usual daily activities and advised to abstain vigorous physical activities during the monitoring period. At the same time, they were instructed to maintain an event record sleep diary. The pressure device was programmed for reading every 30 minutes from 0501h to 2200h (day time) and every 60 minutes from 2201h to 0500h (night-time). The average systolic and diastolic BP values during day and night were taken into consideration. Patients were divided into sub groups by the variation of nocturnal BP fluctuation, as various dipping categories.

Echocardiographic assessment

An individual patient was echocardiographically assessed by two experienced cardiologists independently. LV internal dimensions, inter-ventricular septal (IVS) thickness and posterior wall thickness were measured according to recommendations for cardiac chamber quantification by echocardiography in adults; according to the criteria of American Society of Echocardiography and the European Association of Cardiovascular Imaging [14].

IVS thickness was obtained by zoom 2D guided M-mode standard measurement at the tip of the mitral valve level[12].
LV mass was calculated from the measurements of IVS, posterior wall thicknesses and LV internal diameters according to the Devereux formula[15]; LV mass (Penn) = 1.04 ([Left Ventricular Internal Diameter Diastole(LVIDD) + Posterior Wall Thickness at end-Diastole(PWTD)+Intra Ventricular Septal Thickness at Diastole (IVSTD)]^3- [LVIDD]^3) - 13.6 g].

Determination of Diastolic dysfunction

The diastolic dysfunction was determined by considering the cut off value of septal E/e'(>14), septal e' velocity (<7cm/sec) by Tissue Doppler, TR jet velocity (>280cm/sec) and left atrial volume index (>34mL/m^2)[15]. Further classification of the degree of diastolic dysfunction was made considering E/A ratio (normal 0.8-2) and maximum E velocity at mitral inflow by Pulse Wave Doppler[15] pattern.

Calculation of Ambulatory Arterial Stiffness Index

AASI was calculated as 1 minus the regression slope of diastolic BP plotted against systolic BP obtained through individual 24-h ABPM[16].The specific value for an individual was autogenerated by the ambulatory BP analysis software itself. Normal cull-off was considered as < 0.7[17].

Definitions of ABPM parameters

Twenty fore hour ambulatory BP cut-off was taken as ≥130 mmHg and/or≥80 mmHg [18]. Ambulatory BP day time cut-off was taken as ≥135 mmHg and/or≥85 mmHg whereas night time ambulatory BP cut off was set as ≥120 mmHg and/or≥70 mmHg [18]. The night-to-day BP ratio was calculated by using average nocturnal and daytime BP. Dipping and its categories were 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) [18]. Night time rise of BP (i.e. reverse dipping) was defined as ratio >1.0 [19].

Heart rate non-dippers were defined as those who showed a deduction in heart rate less than 10% between day and night [19].

Statistical Analysis

The results are presented as frequencies and mean ± Standard Deviation (SD). Comparison between the two groups was performed by Student t-test. Categorical variables were compared by chi-square test. Statistical analysis was performed by a commercially available statistical package (SPSS Version 17.0) and p value less than 0.05 was considered as significant.

RESULTS

Characteristics of patient's demography

The study sample included 100 subjects, consisted of 72% (n=72) females and 28% (n=28) of males. The mean age of the study sample was 60.86±8.73 years. Patient's baseline characteristics are illustrated in *Table 1*.

Table 1 Demographic Characteristics of hypertensive patients (n=100)

Variable	Result (n,%)
Age (mean±SD)	60.86 ± 8.73 years
Gender	
Male	28 (28%)
Female	72 (72%)
Pharmacotherapy	
ACEIs	30 (30%)
ARBs	51 (51%)
CCBs	27 (27%)
Diuretics	40 (40%)
Beta blockers	21 (21%)
Alpha blockers	13 (13%)
Co-morbidities	
Diabetes Mellitus	25 (25%)
Dyslipidemia	62 (62%)

ACEIs, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; CCBs, Calcium Channel Blockers

According to ABPM, mean day time systolic BP (SBP) and mean night time SBP was 137±16.55 mmHg and 127.93±18.41 mmHg respectively. The mean day time diastolic BP (DBP) and the mean night time DBP was 79.87±11.12 mmHg and 73.40±11.24 mmHg respectively. Characteristics of the ABPM and heart rate profile are illustrated in *Table 2.*

Table 2 The ABPM and Heart Rate in the study group (n=100)

Parameters	Mean ± SD
24-hour average SBP (mmHg)	135.37 ±16.29
Daytime average SBP (mmHg)	137.00 ±16.55
Night-time average SBP (mmHg)	127.93 ±18.41
The percentage of night-time SBP reduction (%)[a]	6.62
24-hour DBP (mmHg)	78.66 ±10.83
Daytime DBP (mmHg)	79.87 ±11.12
Night-time DBP (mmHg)	73.40 ±11.24
The percentage of night-time DBP reduction (%)[b]	8.10
24-hour HR (/min)	71.85 ±10.42
Daytime HR (/min)	73.20 ±10.56
Night-time HR (/min)	65.81 ±10.67
The percentage of night-time HR reduction (%)[c]	10.09

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. [a] (Daytime SBP-Night-time SBP)/ Daytime SBPx100
[b] (Daytime DBP-Night-time DBP)/ Daytime DBPx100 [c] (Daytime HR-Night-time HR)/ Daytime HRx100. Daytime: 7 AM-10 PM, Night-time 10 PM-7 AM for ABPM purpose

Nocturnal BP dipping pattern

In the sample, 32% (n=32) had normal dipping patterns. Out of the 68% (n=68) with abnormal dipping, 45% (n=45) had sub optimal dipping and 19% (n=19) had reverse dipping. There were 4% (n=4) of patients had extreme dipping pattern as well.

Prevalence of Nocturnal Hypertension and Isolated Nocturnal Hypertension

There were 73% (n=73) patients had Nocturnal Hypertension (NH), 45% (n=45) had day-night sustained hypertension and 02% (n=2) had isolated daytime hypertension. There were 31% (n=31) had Isolated Nocturnal Hypertension (INH). There were only 26% (n=26) with normotension in the study sample.

Association of Ambulatory BP parameters to Echocardiographic Interventricular Septal thickness

There were 82% patients had LV hypertrophy by IVS thickness. There were 48% had mild LVH (11 mm to 13mm), 27% had moderate LVH (14mm to 16mm) and 7% had severe LAH (>17 mm). Ambulatory BP uncontrolled group had a higher IVS thickness compared to ambulatory BP control group, which is statistically significant (p= 0.02). Addition to that, IVS thickness had a positive correlation with 24-hour average ambulatory systolic BP (r=0.3, p<0.01) and 24-hour average ambulatory diastolic (r=0.28, p<0.01) BP, *(figure1)*

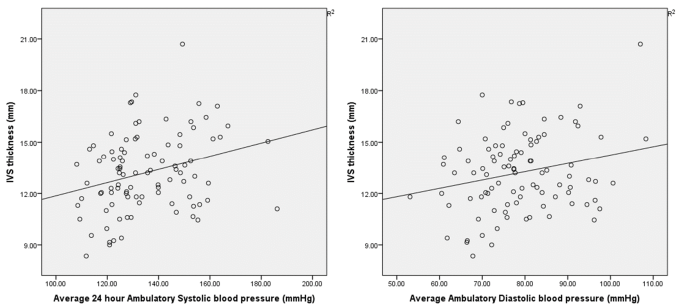

Figure 1 Correlation of IVS thickness with average ambulatory systolic and diastolic BP (IVS- Intra Ventricular Septum)

Association of Ambulatory BP parameters to Echocardiographic Left Ventricular Mass

There was a statistically significant higher LVM noted in ambulatory BP uncontrolled group compared to ambulatory BP controled group 154.9±37g versus 139.6±36.62g (p<0.001). Addition to that, patient with presence of nocturnal hypertension 145.9±42g versus 120±52.7g (p=0.015) was significantly associated with higher LVM. There was a significantly positive relationship between average day time systolic BP and LVM (r = 0.29, p < 0.006) and average nocturnal systolic BP r=0.34, p=0.009)*(figure 2*). Similarly, there was a statistically significant positive correlation between day time average diastolic BP and LVM (r=0.269, p=0.008) and average nocturnal diastolic BP (r=0.4, p=0.024),*(figure3)*

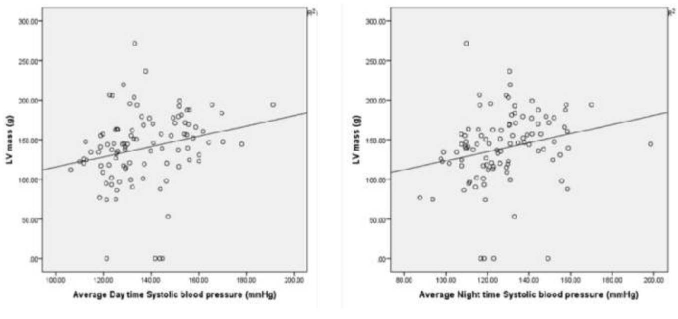

Figure 2 Correlation of LV mass with average day and night systolic BP

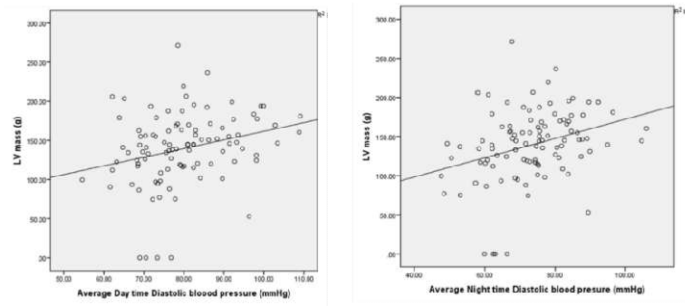

Figure 3 Correlation of LV mass with average day and night diastolic BP

Prevalence of Diastolic dysfunctions

In the study sample, there were 38% (n=38) had any type of diastolic dysfunction. Among them 23.68% (n=9) and 76.31 % (n=29) had grade I and II diastolic dysfunction respectively. However, the prevalence of diastolic dysfunctions among nocturnal hypertensives versus nocturnal normotensives (p=0.28) and dippers versus non-dippers (p=08) was statistically not significant.

Ambulatory Blood Pressure derived Ambulatory Arterial Stiffness Index

There were 88% with AASI less than 0.7 and 12% with AASI more than 0.7, which was abnormal. The value of AASI was significantly higher in ambulatory BP uncontrolled group than ambulatory BP controlled group 0.51±0.14 versus 0.41±0.15 (p=0.001). In contrast, the difference between AASI was not statistically significant among BP controlled and BP uncontrolled groups according to manual clinic BP 0.52±0.14 versus 0.45±0.16 (p=0.808). AASI had a positive correlation with 24-hour average systolic BP (r=0.20 p=<0.001), average nocturnal systolic BP (r=0.357, p<0.001) and average pulse pressure (PP) (r=0.562, p<0.001),*(figure 4).*

0.484±0.166, p=0.02). However, there was no significant difference of IVS thickness (13.59±2.35 mm versus 12.82±2.29 mm, p=0.832) and LV mass (144.83±42.94g versus 143.26±36.92g, p=0.939) observed between HR non-dippers versus dippers.

DISCUSSION

Arterial hypertension is generally associated with a wide spectrum of geometric adaptation of the cardiovascular system as a response to systemic hemodynamics and ventricular load[20]. Left ventricular hypertrophy, diastolic dysfunctions and increased large arterial stiffness are some of the well-recognized such markers [21]. These indices also well correlate with hypertension related adverse cardiovascular events, mainly of coronary artery disease, heart failure and strokes [22]. Therefore, it is important to identify the specific BP parameters that have direct relationship to these various geometric adaptations of the cardiovascular system.

Ambulatory BP parameters and altered left ventricular geometry

In our study, majority of ambulatory BP uncontrolled group had LVH by IVS thickness and both average ambulatory systolic and diastolic BP variables are strongly correlated with the degree of IVS thickness.

Similar findings were observed by *Noa Eliakim-Raz et.al*. [23] in their study. Though, their special interest had been payed even on the patients with normal or near normal IVS or posterior wall thickening for further close follow up. Addition to that, comparable results were observed even in children with chronic hypertension [24].

In the study sample, LVM also behaved in similar pattern to IVS thickness.

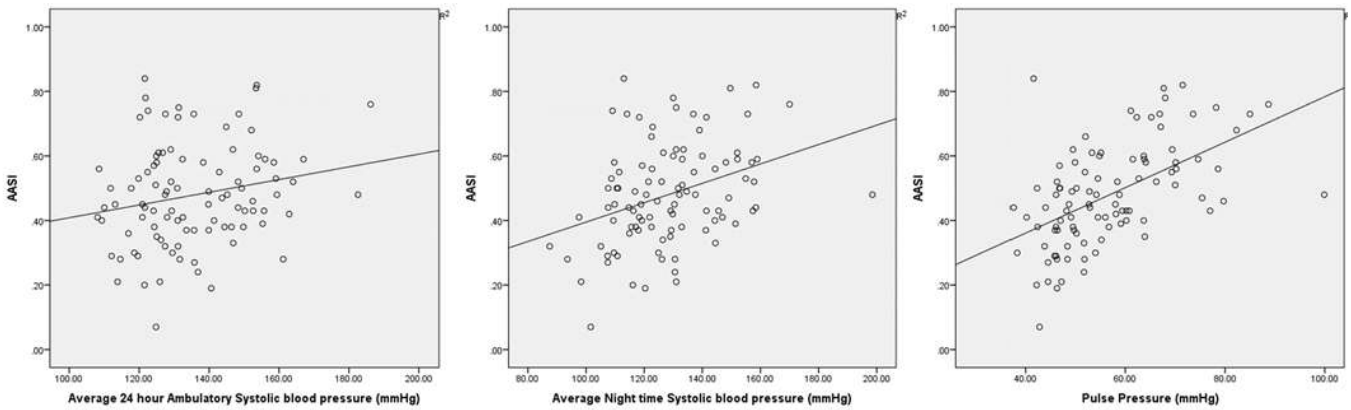

Figure 4 Correlation of AASI with average 24 hour ambulatory systolic, night time systolic BP and pulse pressure

Heart rate variability of the study sample

The average ambulatory HR of the study sample was 71.85 ±10.42 /min. They had an average daytime HR of 73.20 ±10.56 /min and average night-time HR of 65.81 ±10.67 /min. The percentage of night-time HR reduction of the study sample was 10.09%. *(Table 2)*

HR non-dippers, defined as those who showed a nocturnal dip in HR of less than 10% of the day time value[6], accounted for 47% (n=47) of the subjects. In case of HR non-dippers, had significant AASI compared to HR dippers (1.94±6.57 versus

Interestingly we have demonstrated, there is a higher LVM observed among patients with nocturnal hypertension. Parallel observation had been made by *Hang Zhu et al* [25] among chinese population as well. However, they have made the comparison by LV mass index, which is more sensitive rather than LVM performed in our study[25].

The study results have demonstrated that, these adverse LV geometric changes may well correlate with general ambulatory BP parameters as well as specific measures such as nocturnal hypertension. Since the LVH is directly related to the cardiovascular prognosis of a hypertensive patient[26], the ambulatory BP parameters may also have a strength on the determination their prognosis. Additionally, it also highlights the importance of the practice of ambulatory BP monitoring in essential hypertensives though it is under-utilized in most of our current clinical setting.

Diastolic dysfunction

Diastolic dysfunction has gained increasing interest among the hypertensives in current era of cardiology. It may ultimately progress into heart failure with preserved ejection fraction[27] and determines the prognosis of an individual in many aspects. In our series, diastolic dysfunction is observed in 38% among essential hypertensives. However, *M. Fischer et al*. had shown in their series, the prevalence of diastolic dysfunction was 15%[28]. In our observations, there are no significant deference of the occurrence of diastolic dysfunction noted in relation to specific sub-categories of ambulatory BP profile, such as dipping or nocturnal hypertension. However, *Mustafa Aydin et al.* had demonstrated that, in non-dippers, diastolic LV function had been reduced significantly among hypertensives [29].

Our study has discovered that, there is a higher prevalence of diastolic dysfunction observed among our hypertensive patients though no major association is noted in relation to ambulatory BP profile and the prevalence of diastolic dysfunctions. Since that, further research will be helpful to elucidate the pattern, prevalence and especial association of diastolic dysfunction in our hypertensive population as large-scale multicenter studies.

Ambulatory Arterial Stiffness Index

Several authors had been suggested that AASI can be considered as a composite index reflecting cardiovascular hemodynamic properties [30]. The *Reriani MK et al*[31]. showed that AASI could predict cardiovascular mortality beyond classical vascular risk factors. Moreover, the presence of hypertension may alter the large arterial compliance, and it is increasingly being discovered that arterial stiffness is one of the most important marker contributing to the development of many future cardiovascular complications.[30]

In our study, AASI is found to be significantly higher in ambulatory BP uncontrolled group and it is well correlated with ambulatory systolic BP parameters and pulse pressure. Similar observation had been made by *Tingli Qin et al*[32]. among patients with grade I and II essential hypertension.

In summary, the analysis of the dynamic relation of ambulatory BP parameters appears to be a promising new approach in evaluating cardiovascular risk and prognosis related to patients with essential hypertension.

CONCLUSION

Occurrence of altered LV geometry, as a marker of cardiac remodeling in hypertension, best correlates with several ambulatory BP parameters. Similarly, AASI which may link to large arterial stiffness also well correlates with ambulatory BP parameters. Therefore, evaluation of BP by ambulatory monitoring can be used as a one of a sensitive tool for the evaluation of hypertensive cardiac remodeling and finally the prognosis.

Limitations

One of a possible limitation of our study is the convenient sampling method. Addition to that subgroup analysis of BP characteristics depends on specific conditions i.e. diabetes mellitus, obesity etc. was difficult to assess as a result of relatively small sample size. Comparison of the different pharmacological agents into the patients BP profile would make more sensitive outcomes, however due to inadequate numbers in each individual drug class hindered the analysis of that aspects.

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Conflict of interest

The authors declare no conflict of interest whatsoever arising out of the publication of this manuscript.

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