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Ambulatory Blood Pressure Control Pattern in Hypertensive Patients at Tikur Anbesa Specialized Hospital: a cross sectional study

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Acronyms and Abbreviation

BP - Blood Pressure

ABPM - Ambulatory Blood Pressure measurement

OBP - Office Blood Pressure

SBP - Systolic Blood Pressure

DBP - Diastolic Blood Pressure

CCB - Calcium Channel Blocker

ACEI - Angiotensin Converting Enzyme Inhibitors

ARB - Angiotensin Receptor Blockers

HCT - Hydrochlorthiazide

BB - Beta Blocker

DM - Diabetes Mellitus

HTN - Hypertension

GE - General Electric

CS - Cardio Soft software

MUCH - Masked Uncontrolled Hypertension

SPSS - Statistical Package for the Social Sciences

ESC - European Society of Cardiology

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Abstract

Background: Hypertension is the most common cardiovascular problem globally with a particularly increasing burden in developing countries like Ethiopia. Ambulatory blood pressure (ABPM) is superior to office blood pressure (OBP) measurement for diagnosing, prognosticating and following treatment efficacy for hypertension. There is no available data on ABPM control pattern in Ethiopians. This study will determine the ABPM control patterns in Ethiopian hypertensive patients on treatment.

Material and Methods: This was a cross sectional study in hypertensive patients at Tikur Anbessa Specialized Hospitals outpatient departments carried out during January to May 2021. ABPM values of 244 consecutively sampled patients were analyzed. All patients had their BP monitored over 24 h with a Tonoport V (GE CS V6 71), and the data was interpreted using GE CardioSoft™ ABPM software in accordance with European Society of hypertension guidelines. Ethical clearance was given by Addis Ababa University Institutional Review Board and the study was conducted in compliance to standard ethical guidelines.

Results: The study involved 244 adult hypertensive patients; mean age of the patients was 59.4 years and, 54% were females. 58.6% of patients had controlled OBP, while only 45.1% had controlled ABPM. The mean OBP was 137 (19)/81 (10) mmHg and mean 24-hr ABP was 137 (16)/81 (10) mmHg; mean daytime BP was 136/79 ± 17/11 mmHg; mean night-time BP, 138/84 ± 16/11 mmHg. Mean ABPM values were not significantly different between men and women. Comparison of ABPM values with OBP revealed high prevalence of the white coat effect (32%) and masked uncontrolled hypertension (46%). Presence of comorbidities particularly diabetes predicted poor ABPM control.

Conclusion: More than half of patients had uncontrolled BP as per ABPM criteria and significant discrepancy exists between ABPM and

OBP in assessing adequacy of BP control. Guiding management decisions using ABPM can improve BP control rates.

BACKGROUND

Hypertension defined as a systolic and/or diastolic blood pressure $\geq 140/90$ mmHg, is the most common cardiovascular disease globally. It is a major cardiovascular risk factor and a leading risk factor for global deaths. Raised BP remains the leading cause of death globally, accounting for 10.4 million deaths per year (Global Burden of Disease, 2018). When reviewing global figures, an estimated 1.39 billion people had hypertension in 2010. The highest prevalence of raised blood pressure was seen in the African Region (27%).(1)

In Ethiopia, 16 % of the adult population has raised blood pressure with similar prevalence seen in males and females. The overwhelming majority of hypertensive Ethiopians do not take any blood pressure lowering medication. Of those patients on treatment only 53 % had controlled hypertension.(2)

It has been well recognized that office BP measurements have significant limitation in diagnosing and prognosticating hypertensive patients. Among the more precise methods of BP measurement, 24-hour (ambulatory) BP measurement has gained a wide acceptance. Ambulatory blood pressure monitoring generates much more information than the single (typically daytime) 'snapshot in time' reading yielded by clinic measurement by providing a profile of blood pressure behavior over a 24-hour period and blood pressure response to antihypertensive therapy in this period. It also allows more fine-tuned assessments during specific windows of this time cycle i.e. day vs. nighttime control. Night time blood pressure, nighttime dipping pattern and morning surge are important measures of this circadian variation and have significant prognostic implications.(3)

Achieving adequate blood pressure target in hypertensive patients is a difficult task even in the best of setups whereby half of the treated patients have uncontrolled BP(4). The prevalence of uncontrolled hypertension is even higher in developing countries where close to two thirds of patients on treatment fail to achieve targets and this contributes to worsened outcomes including premature death according to a recent review. Even among African countries, eastern African countries have the lowest proportion of treated patients and control rate.(5) A recent multi-center cross sectional study in Ethiopia showed that the rate of uncontrolled hypertension reaches up to 67% in patients on treatment for hypertension. (6)

A white-coat effect can also occur in patients with treated hypertension, and is particularly relevant to the evaluation of patients with possible resistant hypertension. Nearly 30- 40% of patients with uncontrolled office BP have controlled blood pressure on ambulatory blood pressure monitoring.(7) In a larger Spanish study of over 8,200 patients with resistant hypertension, 38% were attributed to white-coat effect based on ambulatory blood pressure monitoring. Profile. (8)

On the other end of the spectrum, a masking phenomena occurs in hypertensives on treatment who apparently have normal office BP but ABPM values reveal poor control and is termed Masked Uncontrolled Hypertension (MUCH). Prevalence rates of up to 30 % are reported in multiple ABPM studies.(9)

Discrepant rates of controlled BP have been reported with ABPM vs conventional BP in some populations.(10)(11)

METHODS

The Ethics Committees of Addis Ababa University, Tikur Anbesa Specialized Hospital, Ethiopia, approved the study protocol and consent form (Dr. Adamu Adissie, Addis Ababa University Institutional Review Board chairperson). The participants gave informed written consent to the study. The study was conducted in accordance with the standard international and national scientific and ethical guidelines.

It is a cross sectional study, with data collected between January 2021 to May 2021. The study population consists of adult hypertensives 18 years and above at renal and cardiac clinics of TASH, who gave consent to be part of the study. Participants were consecutively recruited, demographic data, medical history, imaging, laboratory, and treatment history were collected from the electronic medical record.

OBP was measured in both arms with an oscillometric BP device, while the patient was sitting. The arm with the higher reading was taken as the patients BP after an average of three readings. Systolic and diastolic (Phase V) BP were determined to the nearest 2 mmHg in accordance with European Society of Hypertension recommendation. Ambulatory BP was measured with the Tonoport V monitor (GE CS V67) for a minimum of 24 h, using a similar sized cuff as was used in the OBP measurement. The ABP monitor measured BP at 30-min intervals for 24 hours; from 0600 h to 2200 h (representing daytime) and from 2200 to 0600 h (representing night-time). Participants kept a diary card for the duration of the record to note bedtime and waking time to define day and night and to check the transition time. ABPM data were interpreted in accordance with ESC Hypertension guidelines.

STATISTICAL ANALYSIS

ABPM data processing was performed using the GE Cardiosoft™ Ambulatory Blood Pressure software (PAR Medizintechnik GmbH Sachsendamm D-10829, Berlin, Germany). Data was collected using the electronic data collection system (ODK Collect). This data was converted into excel format via the ODK briefcase software.

Management of data and Statistical analysis was performed using the SPSS software package for Windows version 20 (SPSS Inc., Chicago, IL).

Baseline demographic data was analyzed using descriptive statistics. Correlation between predictor variables like age and office BP with the outcome variable (ABPM values) was analyzed by pearson-spearman coefficients. Factor analysis was used to identify representative laboratory variables in each category.

Comparison between groups (by sex, type of medication, type of comorbidity and OBP control status and number of HTN drugs) for ABPM values was done using the parametric variance tests (Two-tailed Student T test and 1 way ANOVA). The non - parametric tests (chi square and kappa measure of agreement) were used to compare patients based on sex, type of anti-hypertensive medications ,type of comorbidity and OBP control status with 24 hr ABPM ,mean day and mean night BP control status. Proportions were reported as percentages and compared between groups with Chi-square. A p-value less than 0.05 is considered statistically significant.

5. RESULTS

The study involved 244 adult hypertensive patients having followed at TASH cardiac or renal clinics. The mean age of the cohort was 59.4 years, and 54% of subjects were female. Significant proportion of

patient had comorbidities with 29 % of patients having diabetes, 56% dyslipidemic or on statin therapy, and 16 % having IHD. Majority of patients (65%) were taking more than 1 anti-hypertensive drug (Table 1).

Table 1. BASELINE DEMOGRAPHIC DATA

PARAMETER	Number of Patients	percentage of Patients
total patients	244	
Mean Age (years)	59.4 years	
Females	132	54%
<i>Type of anti-hypertensive</i>		
CCB	150	61.5
ACEI	147	60.2
ARB	19	7.8
HCT	63	25.8
BB	75	30.7
Other anti-HTN	21	8.6
<i>Number of anti-hypertensives</i>		
1	83	34
2	91	37
3	55	23
4	13	5
5	1	.4
<i>COMORBIDITY</i>	NUMBER	PERCENT
DIABETES	70	28.7
DYSLIPIDEMIA	136	55.7
STROKE	5	2
IHD	38	15.6

Baseline laboratory and imaging data from echocardiography, doppler ultrasound of peripheral vessels and electrocardiogram revealed the extent of comorbidities and hypertension mediated target organ damage (Table 2).

Table 2. Baseline laboratory and imaging parameters

Parameter	N	Minimum	Maximum	Mean	Std. Deviation
creat	114	0.6	11	.97	1.132
fbs	165	60	413	123.39	44.754
hga1c	56	4	138	9.20	17.594
tc	164	100	321	170.51	48.632
ldl	155	26	238	120.66	40.721
hdl	168	18	96	46.79	11.545
tg	167	42	469	133.98	68.772
sv1_rv5_6	5	1	4	2.80	1.095
ravl	5	1	3	1.40	.894
ivs_thickness	124	6	16	11.32	2.207

BP control was suboptimal as shown from the mean of both OBP 137 (19)/81 (10) mmHg and 24-h ABP 137 (16)/81 (10) mmHg. Rates of controlled BP were 58.6% for OBP, 45.1% for mean 24-h ABPM and only 21.7 % for mean night time BP (Table 3).

Table 3. Results of ABPM and OBPM

	sample	min	max	Mean	SD
Office SBP	244	90	200	137.52	19.058
Office DBP	244	60	120	81.30	10.929
Mean 24hr DBP	244	60	120	80.95	10.371
mean_day_SBP	244	102	198	135.45	17.576
mean_day_DBP	244	60	120	79.30	11.075
mean_night_SBP	244	100	198	138.41	16.247
mean_night_DBP	244	62	125	84.09	11.546
maximum 24hr SBP	244	113	260	191.00	30.145
Maximum 24hr DBP	244	66	130	114.44	10.836
minimum_24_SBP	244	80	225	100.36	16.355
Minim_24_DBP	244	60	127	64.37	8.519

The proportion of patients with controlled BP was different as per the office and ambulatory blood pressure recordings. This proportion also differs based on the period of the ABPM studied for both sexes (Table 4).

Table 4. Proportion of controlled ABPM and OBPM by sex

Parameter	Male	Female	total	Number (total=244)
OBP controlled	59.8	57.6	58.6	143
24hr controlled	42%	47%	45.1	110
Day time controlled	53.6%	58.3	56.1	137
Night time controlled	19.6	23.5	21.7	53

Correlation studies done using Pearson product-moment correlation coefficient revealed significant correlation of age, and OBP values with ABPM values.

The relationship between age and diastolic BP was investigated using Pearson product-moment correlation coefficient. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. There was a Small, negative correlation between the two variables, $r = -.0.21$, $n = 244$, $p < .001$, with increasing age associated with lower DBP Levels.

An independent-samples t-test was conducted to compare the ABPM results for males and females. There was no significant difference in mean ABPM values between males (24 hr SBP = 137(14)/82(10) and females (24 hr SBP = 136(17)/80(11); $t(242) = 0.46$, $p = .65$, two-tailed).

The magnitude of the differences in the means (mean difference = .95, 95% CI: -3.10 to 5.01) was non significant.

Comparison between patients with and without Comorbidities showed significant difference in ABPM measurements.

- Diabetics had higher 24hr systolic ABPM values compared to non diabetics (Diabetic 24hr SBP = 141(17)/81(12) vs non diabetic (24 hr SBP = 134(15)/80(10); $t(241) = 2.8$, $p = .005$, two-tailed). The magnitude of the differences in the means (mean difference = 6.5, 95% CI: 1.99 to 10.99) was significant. Similar results were seen for day and night SBP but not DBP.
- Dyslipidemia patients had significantly higher systolic ABPM . dyslipidemic pt 24 hr SBP = 139(17)/81(10) vs non dyslipidemics (24 hr SBP = 134(14)/80(10); $t(241) = 2.2$, $p = .029$, two-tailed). The magnitude of the differences in the means (mean difference = 4.5, 95% CI: 0.4 to 8.6) was significant. Similar result was seen for day time SBP but not night SBP or DBP.
- Patients with IHD also had poorer 24 hr systolic ABPM control (IHD patients 24 hr SBP = 142(18)/82(8) compared to patients without IHD (24 hr SBP = 136(16)/81(11); $t(242) = 2.0$, $p = .046$, two-tailed). The magnitude of the differences in the means (mean difference = 5.7, 95% CI: 0.1 to 11.4) was significant. Similar result was seen for day time SBP but not night SBP or DBP.

ABPM values were compared based on **Type of anti-hypertensive** drugs patient used. ARB users had poor day time SBP and DBP control. Day time ABPM in ARB users SBP = 147(23)/87(14) vs patients without IHD (24 hr SBP = 134(17)/78(10); $t(242) = 3.0$, $p = .003$, two-tailed). The magnitude of the differences in the means (mean difference SBP = 12.5, 95% CI: 1.1 to 24 and DBP Mean = 8.2 95% CI= 1.2-15.2) was significant. Subgroups were compared based on the Number of anti-hypertensive

medications they used by the one way analysis of variance test and no difference was seen.

Patients with controlled OBP status had better ABPM values compared with those having uncontrolled OBP.

Chi square test for independence with Yates' Continuity Correction was done to compare groups with respect to control status of their ABPM measurements as per the current guidelines.

A chi-square test for independence (with Yates' Continuity Correction) indicated no significant association between gender and ABPM control status, $\chi^2 (1, n = 244) = .59, p = .44, \phi = -.058$. Office BP values showed medium correlation with ABPM; the strongest positive correlation was seen between office DBP and mean night DBP , $r = -.035, n = 244, p < .001$, with increasing Office DBP associated with HIGHER mean night DBP Levels.

OBPM control status had statistically significant but small degree of association of with 24hr ABPM control status ($\chi^2 (1, n = 244) = 9.8, p = .002, \phi = .021$.), but was not correlated with night BP control status (Table 5).

Table 5. Correlation and Discrepancy between ABPM and OBP control

Parameter	Controlled OBP	UnControlled OBP	P value	Phi
Controlled 24 hr ABP	53.8 %	32%(White coat effect)	=0.002	0.21
Uncontrolled 24 hr ABP	46.2% (masked uncontrolled BP)	68%		

Kappa measure of agreement showed Weak correlation between OBP and 24 HR ABPM control status(kappa=0.2 with $p < 0.001$). OBP was able

to predict controlled BP as per 24 HR ABPM with sensitivity of 70% and specificity of 50%.

Among the comorbidities, DM was inversely related with 24hr ABPM control status, $\chi^2 (1, n = 244) = 10.6, p = 0.005, \phi = 0.20$, albeit to a small degree. Other comorbidities had no significant correlation with ABPM status. The class of anti – hypertensive drug used by patients had no significant correlation with ABPM control status.

DISCUSSION

This study is a descriptive study of ABPM conducted in Ethiopia. The results showed that only 45.1 % of patients had controlled BP by ABPM compared to 58.6 % based on OBP, suggesting that OBP could be over-estimating BP control in our setup. This lower rate of BP control by ABPM vs OBP in hypertensive patients on treatment has been documented in previous studies. It has been shown that the degree of OBP reduction is higher than ABPM reduction with treatment.(12) Schmieder et al noted that patients with higher pretreatment SBP levels had an even greater disproportional reduction in office SBP than in ambulatory SBP after undergoing antihypertensive treatment; in addition, these investigators noted that the white-coat effect decreased by $\approx 10/5$ mmHg on average after beginning antihypertensive treatment, thus contributing to the reduction of in-office BP but not in ABPM. Perhaps of equal importance, a morning recording of normal in-office BP may be at peak levels of medication while trough levels later in the day and night may be associated with hypertensive BP values seen with ABPM(13).

Significant discrepancies exist in the ability of OBP in predicting adequate ABPM control as 32% of our patients with controlled ABPM status are misclassified as having uncontrolled OBP. This scenario of white coat effect on BP control was seen in other studies. In a study of

over 600 patients with uncontrolled office blood pressure (i.e., >140 mmHg systolic blood pressure or >90 mmHg diastolic blood pressure), nearly 40% of those on one or two medications and almost 30% of those on three medications had controlled blood pressure on ambulatory blood pressure monitoring (7). In a larger Spanish study of over 8,200 patients with resistant hypertension, 38% were attributed to white-coat effect based on ambulatory blood pressure monitoring. The true resistant hypertensive patients were younger, more frequently men, with a longer duration of hypertension and a worse cardiovascular risk profile. The group included larger proportions of smokers, diabetics, target organ damage (including left ventricular hypertrophy, impaired renal function, and micro albuminuria), and documented cardiovascular disease (8). Muxfeldt et al., in a cohort of 286 hypertensive subjects with uncontrolled BP, found that 43.7% had white coat RH, (office BP > 140/90 mmHg and daytime BP < 135/85 mmHg) and less target organ damage compared to the true resistant hypertensives (14).

This similar finding from the above studies in different populations confirm the limitations of OBP in assessing adequacy of BP control, which can ultimately lead to unnecessary treatment escalation with possible increase in side effects.

On the other end of the spectrum, patients with apparently controlled OBP can have unmasking of their poor BP control during ABPM. In our study, 46.2 % of individuals with controlled OBP were shown to have masked BP elevation (masked uncontrolled hypertension) with 24 hour ABPM. In support, Pierdomenico et al. in a cohort of 742 treated hypertensive subjects, 426 apparently responders and 276 apparently resistant, found that 126 subjects (29.5% of the apparently responders) had masked hypertension and 146 (52.8% of the apparent resistant) had white coat RH. In the same study, in the follow-up period

cardiovascular risk was higher in masked hypertensives (masked versus responder hypertensives, relative risk (RR) 2.28, 95% confidence interval (CI) 1.1–4.7,) and in true resistant hypertensives (true resistant versus responder hypertensives, RR 2.94, 95% CI 1.02–8.41,) (9).

A similar study from Egypt revealed 33.2% of apparent responders by OBP had masked uncontrolled hypertension (MUCH) according to 24-h ABPM criteria (15). This study also showed the dominant contribution of nocturnal hypertension for MUCH, which was solely attributable to an elevated nocturnal BP almost double that due to daytime BP elevation (57.3% vs. 27.1%, $P < 0.001$). Our study also showed the dominant contribution of nocturnal hypertension for MUCH compared to day time BP elevation (75% vs 36%).

Our study shows that half of our study population had uncontrolled BP by both OBP and ABPM criteria. Similarly, only 40% of patients had controlled OBP in a recent Ethiopian study (6). Suboptimal BP control has been reported in other many studies worldwide; in India, uncontrolled BP was found to be 62.3 %; and in the USA, 51.2% of the participants were found to have uncontrolled BP(16).

These data show the poor efficiency of current HTN management throughout the range of healthcare facilities at different levels of development.

There was no difference in ABP control status between the sexes. Increasing age was associated with lower DBP values as would be expected from the vascular changes related to ageing starting from the 6th decade. This changes in BP was first shown in the Framingham heart study.

In our study, Diabetic patients were shown to have significantly higher 24 hour and night time ABPM values and lower rate of ABPM control

status compared to non diabetics. This has been shown in ABPM studies done on diabetics. WCH seems to be less frequent, and masked HTN is more frequent in diabetic patients and seems to be associated with increased organ damage(17).

Dyslipidemic patients and those with IHD also had significantly higher mean 24 hour and day time SBP values. Similar trends have been reported in other studies done using ABPM.

In an Italian study it was shown that the true resistant hypertensive patients had a worse cardiovascular risk profile. The group included larger proportions of smokers, diabetics, target organ damage (including left ventricular hypertrophy, impaired renal function, and micro albuminuria), and documented cardiovascular disease (8).

Among the treatment agents, ARB users had higher mean ABPM value. This is likely related to very small number of patients using ARB affecting the statistical analysis. **The number of medications** used did not result in significant difference of BP control in our study. Number of antihypertensive medications was not significant determinant of treatment efficacy in our study. Similar findings were noted by Pierdomenico et al. where percentage of subjects receiving single, double, and multiple therapy was not different between responder and masked hypertension (58.2% v 62.7%, 28.2% v 26.2%, and 13.7% v 11.1%, respectively, P =not significant [NS]). Drug classes were not different. Use of three or more drugs was not different between the false and true resistant groups (85.6% v 89.2% and 14.4% v 10.8%, respectively, PNS), and drug types were not different (about 90% in each group received a diuretic)(9).

CONCLUSION

This study shows the high burden of uncontrolled BP in this cohort. It also shows the significant advantages of ABPM in assessing adequacy of BP control with additional BP parameters of prognostic importance and complementary to OBP can help clinicians for more informed decision making . The increased prevalence of uncontrolled BP status in patients with comorbidities like diabetes shows the need to increase the use of ABPM in this high risk population. Further studies to incorporate more patient cohorts with prospective models can further elucidate the role of ABPM in our setup.

Declarations

- **Ethics approval and consent to participate** – The Ethics Committees of Addis Ababa University, Tikur Anbesa Specialized Hospital, Ethiopia, approved the study protocol and consent form (Dr. Adamu Adissie, Addis Ababa University Institutional Review Board chairperson). The participants gave informed written consent to the study. The study was conducted in accordance with the standard international and national scientific and ethical guidelines.

- **Consent for publication** – obtained from all patients via informed written consent.
- **Availability of data and materials** - The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request
- **Competing interests** - None
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- **Authors' contributions** – “Muluaem Alemayehu analyzed and interpreted the patient data regarding the ambulatory blood pressure control pattern. All authors read and approved the final manuscript.”
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